university of groningen

University Medical Center Groningen

University of Groningen

Interventions in childhood epilepsy: pharmacotherapy and ketogenic diet

Weijenberg, Amerins

DOI:
10.33612/diss.132700288

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Weijenberg, A. (2020). *Interventions in childhood epilepsy: pharmacotherapy and ketogenic diet*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
https://doi.org/10.33612/diss.132700288

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 05-05-2023

Interventions in childhood epilepsy: pharmacotherapy and ketogenic diet

Amerins Weijenberg

Printing of this thesis was financially supported by the University Medical Center Groningen, Stichting Epilepsie Instellingen Nederland (SEIN), UCB Pharma B.V. and Nutricia.

ISBN
ISBN: 978-94-034-2840-6 (Printed book)
ISBN: 978-94-034-2841-3 (PDF without DRM)

Cover & Lay-out design
www.proefschriftopmaak.nl, Groningen

Print
Scholma Print & Media, Bedum

© 2020, Amerins Weijenberg, Groningen, the Netherlands. All rights reserved. No part of this thesis may be reproduced or transmitted in any form or by any means without the prior permission of the copyright owner.

rijksuniversiteit groningen

Interventions in childhood epilepsy: pharmacotherapy and ketogenic diet

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 23 september 2020 om 12.45 uur

door

Amerins Weijenberg

geboren op 1 maart 1982
te Smallingerland

Promotor
Prof. dr. O.F. Brouwer

Copromotor
Dr. P.M.C. Tijink-Callenbach

Beoordelingscommissie
Prof. dr. K.P.J. Braun
Prof. dr. H.P.H. Kremer
Prof. dr. H.J.M. Majoie

Paranimfen

Bregje Mooren
Ellen Nijkamp

CONTENTS

CHAPTER 1

Introduction

INTRODUCTION

Epilepsy

Epilepsy is a brain disorder that is associated with an increased risk of abnormal excessive or synchronous neuronal activity causing clinical symptoms that may be quite variable depending on the localization and intensity of the abnormal electrical activity. For a long time epilepsy had been defined as having had at least two unprovoked seizures with a minimum of 24 hours in between. In 2014, the International League Against Epilepsy (ILAE) added two conditions for making a diagnosis of epilepsy: 1) in case of one unprovoked seizure, but with a recurrence risk estimated to be at least 60%; and 2) if a specific epilepsy syndrome can be diagnosed.[1] In children, epilepsy is the most frequent chronic neurological disorder having a median incidence of 82.2/100,000 children with a peak during the first year of life.[2, 3] This high incidence in infancy is caused by several factors including epilepsy being an early manifestation of many congenital brain malformations, metabolic disorders and/or other genetic conditions. In addition, due to its physiological properties, the young brain is more vulnerable and less resistant to abnormal epileptic activity.[4] After being at a lower stable level during adulthood, incidence increases again in the elderly with cerebrovascular disease being the most common etiology.[5]

Making a correct diagnosis of epilepsy is essential because it has considerable consequences and great impact on daily life. The diagnostic process should therefore be careful and structured (Figure 1). The first, often most difficult step is to decide whether the event(s) have an epileptic origin. Recently, a prediction model was introduced to facilitate this diagnostic process, using clinical characteristics and electroencephalogram (EEG) reports.[6] If the paroxysmal events are judged to be epileptic seizures, the seizure type must be determined. In 2017, the ILAE revised the operational classification of seizure types (focal onset, generalized onset, unknown onset), allowing greater flexibility and transparency.[7] The next step is to define the epilepsy type (focal, generalized, combined generalized and focal, unknown). The EEG plays an important role in this process of classifying seizure and epilepsy type. Complementary, the etiology of the epilepsy should be determined.[8] In 2010, the formerly used categories idiopathic, symptomatic, and cryptogenic were replaced by genetic, structural/metabolic and unknown cause.[9] In 2017, the structural/metabolic category was separated and the categories infectious and immune were added, making six etiologic groups.[8]

Especially for epilepsies in infancy and childhood, an essential step is trying to define an epilepsy syndrome, which combines seizure type(s), age at onset and EEG characteristics (Figure 1). Most importantly, such a syndrome diagnosis often has major prognostic and therapeutic implications. Examples are focal epilepsy with centrotemporal spikes and West syndrome, being more or less extremes in the epilepsy syndrome spectrum with respect to prognosis and treatability. It is important to realize that a specific syndrome does not necessarily imply a specific etiology. For example, both tuberous sclerosis (genetic) and hypoxic ischemic encephalopathy (structural) may be the underlying etiology in a young child with infantile spasms.

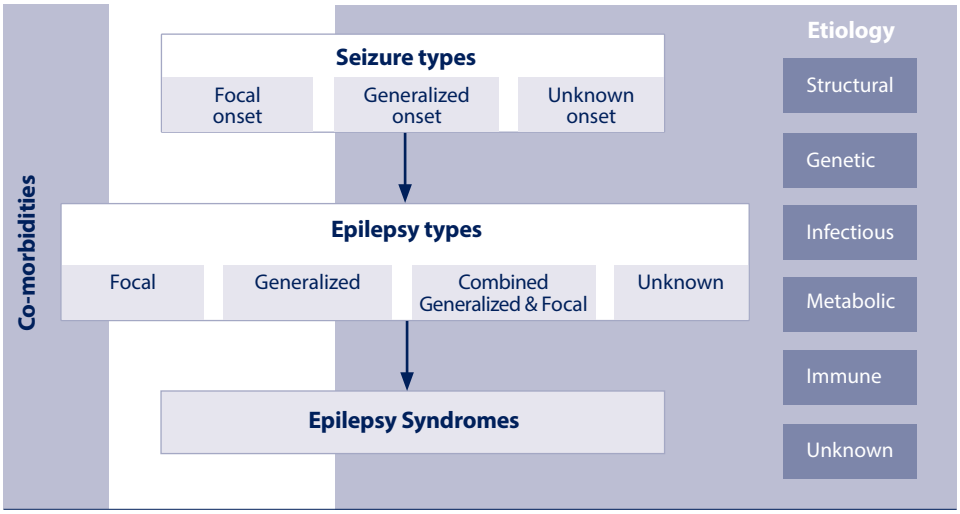

Figure1. Framework for classification of the epilepsies (*ILAE*)[8]

Treatment of epilepsy

The aim of treating children with epilepsy is good/acceptable seizure-control without side effects. For some self-limited epilepsy syndromes with a very low seizure frequency, like focal epilepsy with centrotemporal spikes and early type focal occipital epilepsy (Panayiotopoulos syndrome), treatment is often not necessary. For most children with epilepsy, however, treatment must be considered with antiepileptic drugs (AED) being first choice. It is important to realize that these drugs only suppress seizures and do not influence the course of the epilepsy.[10] Of the children with newly diagnosed epilepsy, 60-70% will become seizure free with first-line monotherapy treatment.[11] When two different AEDs have been consecutively titrated to the maximum dose without reaching adequate seizure control, a combination of two AEDs is recommended.[12]

Still, about 30% of patients with epilepsy (adults and children combined) are more difficult to treat, need polytherapy with higher risk of side effects or do not respond at all.[13] In each child with epilepsy not responding to two first-line drugs, one should consider whether he/she is a candidate for epilepsy surgery. Other non-drug treatment options are ketogenic diet and vagus nerve stimulation (Table 1).

Antiepileptic drugs

Since the end of the 19th century, the number of available AEDs has increased progressively (Figure 2). Bromide was introduced 150 years ago, followed by phenobarbital and phenytoin in the beginning of the 20th century.[14] Although very effective, these drugs had severe side effects mainly involving cognition and behavior. With the introduction of ethosuximide, carbamazepine and valproate in the fifties and sixties of the last century, the treatment of patients with epilepsy improved significantly as these drugs were more safe and less toxic.[15]

Many of these so-called first-generation AEDs are, however, strong inducers or inhibitors of hepatic enzymes, mainly the cytochrome P450 isoenzymes, with an associated risk for drug-drug interactions.[16]

Table 1. The different treatment modalities in children with epilepsy

	Diagnosis	Efficacy	Adverse events[a]
AED	Epilepsy	70% seizure free/acceptable seizure frequency[11]	Dizziness, drowsiness, nausea, headache
Surgery	Intractable focal epilepsy	Seizure free > 1 year: 77%[27] Good outcome: 65%[26]	Motor impairment, Visual field defect, infection
	Lennox-Gastaut syndrome	Corpus callosotomy: 60% seizure free[44]	
VNS	Intractable epilepsy, focal/generalized, not candidate for surgery	>50% seizure reduction: 0-55%[31, 32]	Voice alteration, cough, (throat) pain
KD	Intractable epilepsy, focal/generalized, not candidate for surgery	>50% seizure reduction: 38-50%[34, 35]	Constipation, nausea/vomiting

[a] most common adverse events
AED, antiepileptic drugs; KD, ketogenic diet; VNS, vagus nerve stimulation.

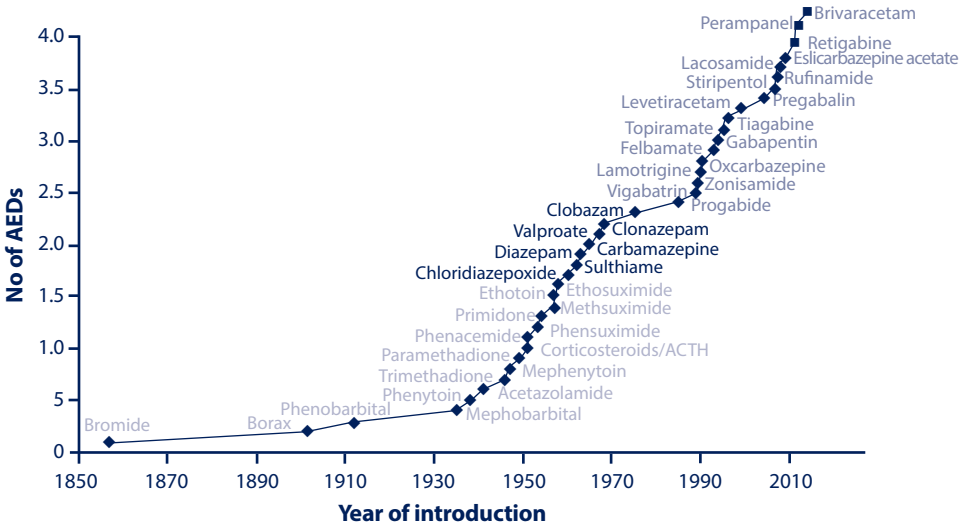

Figure 2. Introduction of antiepileptic drugs *(adapted with permission from Löscher and Schmidt, 2017 [45])*

In the early nineties five major AEDs were licensed: vigabatrin, oxcarbazepine, lamotrigine, felbamate, and gabapentin.[15] The hope was that these so-called second generation AEDs would be at least as effective as the older drugs, but with less side-effects and minimal or no drug-drug interactions.[17] Vigabatrin and felbamate are, however, not routinely prescribed because of toxicity. A few years later, some other AEDs were registered with topiramate and levetiracetam being the most successful ones.

In the last ten years, the AEDs lacosamide, eslicarbazepine acetate, retigabine, perampanel, and brivaracetam were approved. These third-generation drugs still have to proof their value in clinical practice.

Antiepileptic drugs in children

Most new AEDs are initially licensed for focal epilepsy in adults as add-on therapy, and sometimes subsequently registered as monotherapy and/or add-on therapy for different seizure types/ epilepsies. They must be approved by the Food and Drug Administration in the United States of America (FDA) and the European Medicines Agency (EMA), separately. Despite the availability of many new second- and third-generation AEDs, high level evidence for their efficacy and tolerability is lacking,[18] especially as monotherapy in children.[19] New AEDs are available for children only years after their registration for adults, sometimes by extrapolating data from adults, and in most cases only as add-on therapy for certain seizure types and/or epilepsy syndromes.[20] Children are, however, not small adults as they have different pharmacokinetics and pharmacodynamics.[21] New AEDs should therefore be tested in children separately, both as add-on therapy and monotherapy.[22] In general, monotherapy is preferred over add-on therapy because its higher compliance rate and less drug-induced side effects. Only some new AEDs have been formally licensed for monotherapy in children, consequently leading to off-label prescription of certain AEDs in children.[23] Apart from different pharmacokinetics and pharmacodynamics, there is a wide range of different epilepsy syndromes only or mainly occurring in children, each of them having its own preferential treatment strategy. At one end of the spectrum there are self-limited epilepsies not needing treatment with AEDs at all; at the other end the severe epileptic encephalopathies such as West syndrome and Lennox-Gastaut syndrome that have a much less favorable prognosis and are often drug treatment resistant. Although the need for separate trials in children with epilepsy is recognized, also by the International League Against Epilepsy (ILAE), substantiated evidence for the efficacy of AED treatment of children with epilepsy is still scarce.[19]

Epilepsy surgery

Epilepsy surgery is the most effective, potentially curative treatment in both adults and children with pharmacoresistant focal epilepsy, but relatively few patients are good candidates for this therapy.[24] The key of epilepsy surgery is to delineate the epileptogenic zone, despite the absence of a gold-standard biomarker, to ensure a surgical cure.[24] Pre-surgical evaluation exists at least of performing high-resolution MRI, neuropsychological assessment and video-scalp-EEG monitoring. Complementary investigations for better localization of the epileptogenic zone and assessment of the risk of postoperative deficits are optional.[24] Depending on the type and volume of the lesion

and epileptogenic zone, different types of surgery can be performed including anterior temporal lobectomy, lesiotomy, neocortical resection, hemispherectomy, multiple subpial transection and corpus callosotomy. Stereotactic thermo-ablation is an option for very small single periventricular heterotopic nodules.[25] The main outcome measurement for patients who have undergone epilepsy surgery is seizure freedom after one year (with or without AEDs). In an analysis of the efficacy of epilepsy surgery, the Cochrane Epilepsy Group concluded that of the 16,253 reviewed patients (age 0-86 years), 65% achieved a good outcome after surgery with a wide range across studies from 13.5% to 92.5%.[26] Adjacent to its high efficacy, epilepsy surgery often also leads to improvement of cognition, behavior, and quality of life.[24] Epilepsy surgery is considered relatively safe and serious adverse events decreased over the years. In general, permanent neurologic deficit is seen in less than 5% of the operated patients, but this depends on location and type of surgery.[10] In an RCT performed in 116 children, 77% (44/57) were still seizure free one year after epilepsy surgery compared to 7% (4/59) in the drug treatment group.[27] Serious adverse events were seen in 33% (n=19) of the children; those with a hemiparesis did improve, but not to their pre-existent level.[27] A shorter duration of epilepsy prior to surgery and early withdrawal of AEDs after surgery in children with a presumed complete resection and obtained seizure freedom both correlate with better outcome regarding intelligence and it has therefore been advised that every child with an MRI-visible lesional focal epilepsy should be evaluated in a multidisciplinary pediatric epilepsy surgery team.[28] Progress has also been made in identifying patients for epilepsy surgery who have a normal MRI. Mainly due to improved neuroimaging and neurophysiology methods, the epileptogenic zone can be delineated which may qualify them for epilepsy surgery too.[24]

Vagus nerve stimulation

Vagus nerve stimulation (VNS) was approved as add-on therapy for patients with intractable epilepsy in the United States in 1997, initially for patients older than 12 years with focal epilepsy only. Today, VNS can be used for both focal and generalized epilepsy and there are no restrictions regarding age. A device, surgically placed under the skin in the left pectoral area, sends electrical signals to the left vagus nerve through a lead. The frequency, intensity and duration of stimulation must be programmed. Although a guidance with the most common and efficacious settings for each generator model is available, all settings can be personalized for every individual patient.[29] Furthermore, the device can be activated manually with a magnet in acute situations to try to abort seizures. The exact mechanism of action of VNS is unknown, but it may mediate at least some of its effects through the thalamus.[30] The efficacy of VNS in children, defined as >50% reduction of seizure frequency, varies considerably in the different studies that have been performed. Pooled data of 481 children showed a responder rate of 55% (95% confidence interval 51%–59%), but the heterogeneity of the data was significant and studies were uncontrolled.[31] In the only one published blinded RCT on VNS in 41 children with intractable epilepsy no significant difference was observed with respect to the change of seizure frequency.[32] The most common side effects of VNS are voice alteration, increased coughing, (throat) pain and paresthesia; these side effects are mostly mild and transient. One prominent finding is that children are at greater risk of wound infection compared to adults.[31]

Ketogenic diet

Ketogenic diet (KD), a high fat and very low carbohydrate diet, has become one of the non-drug treatment options for children with medical refractory epilepsy, although its mechanism of action is still unclear.[33] Metabolizing a high amount of dietary fat means that ketone bodies become the main energy source for the whole body and the brain. The efficacy of the classical KD for children with refractory epilepsy has been strongly supported by two randomized controlled trials.[34, 35] The classical KD consists of dietary long-chain triglycerides (LCT) and is based on a ratio of 3:1 or 4:1 for fat:(carbohydrate + protein). A KD variant with medium-chain triglycerides (MCT) allows a higher intake of carbohydrates and protein, since MCT produce more ketones per kilocalorie of energy than LCT. This less restrictive MCT diet seems as effective as the classical KD.[36] Also the Modified Atkins Diet (MAD), a less restrictive variant of the classical KD, has shown similar benefits in seizure disorders.[37]

Aim of our studies

The focus of this thesis is on two treatment modalities used in children with epilepsy: pharmacotherapy (part A) and ketogenic diet (part B).

Part A: pharmacotherapy

In **Chapter 2,** we review the randomized controlled trials (RCTs) on second-generation AEDs used as monotherapy in children that had been performed before 2010. We evaluated both the results of these trials and their methodological and clinical validity. Despite the limited evidence for their efficacy, the use of (these) second-generation AEDs in children increased considerably over time.[38-41]

In **Chapter 3,** we report an evaluation of prescribing patterns of AEDs in Dutch children from 2006-2014 and discuss the role of various influencing factors such as guidelines, costs and personal experience.

Especially levetiracetam (LEV) appeared to be quite successful since its introduction on the Dutch market in 2000, also in children.[41] Anticipating on a RCT on LEV monotherapy in children, we reviewed studies on LEV monotherapy in children with epilepsy. The results of this review are presented in **Chapter 4**. We initiated this multicenter RCT in the Netherlands aiming to compare LEV and valproic acid (VPA) as monotherapy in children with newly diagnosed epilepsy, to provide the highest level of evidence for LEV monotherapy in children.[19] Unfortunately, we had to stop the trial prematurely because the recruitment rate was too low. In **Chapter 5**, we critically analyze the reasons for this trial failure and give some recommendations for future studies.

Part B: ketogenic diet

In **Chapter 6**, the basic principles of the KD, and its consequences and problems in emergency situations are reported, with emphasis on the importance of a personalized emergency protocol

for children being treated with KD. Application of KD and its variants has a huge impact on daily life for both child and parents/caretakers, but also for the medical staff.

In **Chapter 7**, the results of introducing an all-liquid KD in an outpatient setting, including its feasibility and timely assessment of efficacy, are presented. In clinical practice, the mean time period before considering discontinuation of the KD because of inefficacy is 3.5 months.[42] A rapid assessment of its efficacy is highly desirable because of the significant impact of the KD on daily life. The use of an all-liquid formulation might contribute to an earlier and more stable metabolic situation and level of ketosis, allowing sooner assessment of efficacy.

In **Chapter 8**, the results of application of the MAD in a very unique group of four young adolescents with North Sea Progressive Myoclonus Epilepsy are described. This is a rare genetic disorder characterized by progressive myoclonus, seizures, early-onset ataxia and areflexia.[43]

In **Chapter 9,** we discuss our studies from a more general perspective. Recommendations are given for future research, ending with some concluding remarks. How can we achieve the best evidence based treatment in every child with epilepsy?

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475-482.
2. Kotsopoulos IA, van Merode T, Kessels FG, et al. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 2002;43:1402-1409.
3. Aaberg KM, Gunnes N, Bakken IJ, et al. Incidence and prevalence of childhood epilepsy: a nationwide cohort study. Pediatrics 2017;139:e20163908.
4. Sander JW and Shorvon SD. Epidemiology of the epilepsies. J Neurol Neurosurg Psychiatry 1996;61:433-443.
5. Stephen LJ and Brodie MJ. Epilepsy in elderly people. Lancet 2000;355:1441-1446.
6. van Diessen E, Lamberink HJ, Otte WM, et al. A prediction model to determine childhood epilepsy after 1 or more paroxysmal events. Pediatrics 2018;142:e20180931.
7. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:522-530.
8. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:512-521.
9. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005-2009. Epilepsia 2010;51:676-685.
10. Benbadis SR, Geller E, Ryvlin P, et al. Putting it all together: options for intractable epilepsy: An updated algorithm on the use of epilepsy surgery and neurostimulation. Epilepsy Behav 2018;88:33-38.
11. Arts WF, Brouwer OF, Peters AC, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 2004;127:1774-1784.
12. Raspall-Chaure M, Neville BG, Scott RC. The medical management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol 2008;7:57-69.
13. French JA. Refractory epilepsy: Clinical overview. Epilepsia 2007;48 Suppl 1:3-7.
14. Shorvon SD. Drug treatment of epilepsy in the century of the ILAE: the first 50 years, 1909-1958. Epilepsia 2009;50 Suppl 3:69-92.
15. Shorvon SD. Drug treatment of epilepsy in the century of the ILAE: the second 50 years, 1959-2009. Epilepsia 2009;50 Suppl 3:93-130.
16. Patsalos PN and Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol 2003;2:347-356.
17. Johannessen Landmark C and Patsalos PN. Drug interactions involving the new second- and third-generation antiepileptic drugs. Expert Rev Neurother 2010;10:119-140.
18. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2018;91:82-90.
19. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551-563.
20. Chung AM and Eiland LS. Use of second-generation antiepileptic drugs in the pediatric population. Paediatr Drugs 2008;10:217-254.
21. Moore P. Children are not small adults. Lancet 1998;352:630.
22. Dulac O. Issues in paediatric epilepsy. Acta Neurol Scand Suppl 2005;182:9-11.
23. Borges AP, Campos MS, Pereira LR. Evaluation of unlicensed and off-label antiepileptic drugs prescribed to children: Brazilian regulatory agency versus FDA. Int J Clin Pharm 2013;35:425-431.

24. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol 2014;13:1114-1126.
25. Cossu M, Fuschillo D, Cardinale F, et al. Stereo-EEG-guided radio-frequency thermocoagulations of epileptogenic grey-matter nodular heterotopy. J Neurol Neurosurg Psychiatry 2014;85:611-617.
26. West S, Nolan SJ, Cotton J, et al. Surgery for epilepsy. Cochrane Database Syst Rev 2015;7:Art. No: CD010541.
27. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for drug-resistant epilepsy in children. N Engl J Med 2017;377:1639-1647.
28. Braun KPJ and Cross JH. Pediatric epilepsy surgery: the earlier the better. Expert Rev Neurother 2018;18:261-263.
29. Wheless JW, Gienapp AJ, Ryvlin P. Vagus nerve stimulation (VNS) therapy update. Epilepsy Behav 2018;88:2-10.
30. Ring HA, White S, Costa DC, et al. A SPECT study of the effect of vagal nerve stimulation on thalamic activity in patients with epilepsy. Seizure 2000;9:380-384.
31. Morris GL 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the guideline development subcommittee of the American Academy of Neurology. Epilepsy Curr 2013;13:297-303.
32. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Dev Med Child Neurol 2012;54:855-861.
33. Hartman AL, Gasior M, Vining EP, et al. The neuropharmacology of the ketogenic diet. Pediatr Neurol 2007;36:281-292.
34. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500-506.
35. Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand 2017;135:231-239.
36. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 2009;50:1109-1117.
37. Porta N, Vallee L, Boutry E, et al. Comparison of seizure reduction and serum fatty acid levels after receiving the ketogenic and modified Atkins diet. Seizure 2009;18:359-364.
38. Ackers R, Murray ML, Besag FM, et al. Prioritizing children's medicines for research: a pharmaco-epidemiological study of antiepileptic drugs. Br J Clin Pharmacol 2007;63:689-697.
39. Cohen SA, Lawson JA, Graudins LV, et al. Changes in anticonvulsant prescribing for Australian children: implications for quality use of medicines. J Paediatr Child Health 2012;48:490-495.
40. Dorks M, Langner I, Timmer A, et al. Treatment of paediatric epilepsy in Germany: antiepileptic drug utilisation in children and adolescents with a focus on new antiepileptic drugs. Epilepsy Res 2013;103:45-53.
41. van de Vrie-Hoekstra NW, de Vries TW, van den Berg PB, et al. Antiepileptic drug utilization in children from 1997-2005 - a study from the Netherlands. Eur J Clin Pharmacol 2008;64:1013-1020.
42. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia 2009;50:304-317.
43. van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by GOSR2 mutation. Mov Disord 2014;29:139-143.
44. Douglass LM and Salpekar J. Surgical options for patients with Lennox-Gastaut syndrome. Epilepsia 2014;55 Suppl 4:21-28.
45. Loscher W and Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia 2011;52:657-678.

PART A:
Pharmacotherapy

CHAPTER 2

RCTs with new antiepileptic drugs in children: a systematic review of monotherapy studies and their methodology

A. Weijenberg, M. Offringa, O.F. Brouwer, P.M.C. Callenbach

Epilepsy Research 2010;91:1-9

SUMMARY

Few randomized controlled trials (RCTs) have been performed in which a second-generation antiepileptic drug (AED) used as monotherapy was compared with placebo or another AED in children (<18 years of age) with epilepsy. We describe the results of the available studies, assess the validity of these results, and give recommendations for optimal study design for AED monotherapy studies in children with epilepsy.

Studies were identified using PubMed (Medline), Embase and the Cochrane Library (January 1990–January 2010). All reports were assessed for methodological quality and results were summarized descriptively.

Nine RCTs were included. No difference in efficacy and safety between second-generation AEDs and first-generation AEDs in children was detected. Considerable heterogeneity in study design, inclusion criteria and primary endpoints impaired formal meta-analysis and correct interpretation of results. Follow-up periods were between 2 and 104 weeks; the dosage of the tested AEDs varied between studies, with sometimes use of apparent subtherapeutic dosages; in only two studies the method of randomization was well described, in only three the power calculations; several studies did not use an intention-to-treat analysis. Although from the available studies first- and second-generation AEDs appear to have similar efficacy and safety in children with epilepsy, these trials are inadequate to provide a sufficient evidence base for decision making. Better trials are needed: AEDs should be studied in optimal pediatric doses, power should be sufficient to detect small but clinically relevant differences, and the follow-up period should be long enough. Most important, primary endpoint to be evaluated should be time to treatment failure or retention rate, since these outcomes combine efficacy and safety.

INTRODUCTION

In children with epilepsy, psychomotor development may be negatively influenced by persistent seizure activity and side effects of the anti-epileptic medication. Good seizure control with no or minimal side effects is the desired endpoint for these children and their families. In some children, first-generation anti-epileptic drugs (AEDs) are insufficient to control seizures or drug-related adverse events may lead to discontinuation of these AEDs. Second-generation AEDs may be more effective and may yield fewer side effects.

In the last 15 years, seven second-generation AEDs have been licensed as add-on therapy for children (Table 1). Six of these have also been licensed as monotherapy: vigabatrin, topiramate, lamotrigine, oxcarbazepine, levetiracetam (only in children over 16 years of age) and gabapentin. Monotherapy treatment is preferred over polytherapy because interactions with other AEDs are not present, and fewer drug-induced adverse events occur, which will improve compliance. Yet, only a few studies have been performed in children with epilepsy comparing the effects of second-generation AEDs used as monotherapy with placebo or other AEDs (both first- and second-generation).[1-9] Most studies on efficacy and safety of second-generation drugs have been performed in adults. The response to AEDs may vary between children and adults due to, for instance, different pharmacokinetics.[10] Also, both the severity and incidence of adverse events may be different in adults and children. Furthermore, there is a wide range of epilepsy syndromes that mainly occur in children, some of them being rather benign, others, like West and Lennox-Gastaut syndrome, having a generally unfavorable prognosis.

The most recent systematic review on second-generation AEDs in children with epilepsy mainly included studies in which AEDs were given as add-on therapy and studies in which second-generation AEDs were not compared with other AEDs.[11] We performed a systematic review in which we describe the results of randomized controlled studies comparing the effects of second-generation AEDs used as monotherapy with placebo or other AEDs and relate these results to the methodological and clinical validity of the trials. Also based on the findings of this review, we give some recommendations for an optimal study design for AED monotherapy studies in children with epilepsy.

Table 1. New antiepileptic drugs in children in Europe

Name	Registration year add-on therapy	License from age	Monotherapy indications	Add–on therapy indications
Felbamate	1995	4 years	NR	Lennox-Gastaut[a]
Vigabatrin	1998	All	Infantile spasms	Partial seizures
Topiramate	1999	2 years	>6y partial seizures and GTCS	Partial seizures, GTCS and Lennox-Gastaut
Lamotrigine	2000	2 years	>2y absences, >12y partial and generalized seizures, Lennox-Gastaut	Partial and generalized seizures, Lennox-Gastaut
Oxcarbazepine	2000	6 years	Partial seizures	Partial seizures
Levetiracetam	2005	1 month	>16y partial seizures	Partial seizures, >12y GTCS and myoclonic seizures
Gabapentin	2007	6 years	>12y partial seizures	Partial seizures

Data from EMEA 2010
[a] if resistant to other antiepileptic drugs
GTCS, primary generalized tonic-clonic seizures; NR, not registered; partial seizures, partial seizures with or without secondary generalization; y, year

METHODS

We included all identified studies in children (<18 years of age) with epilepsy in which any of the following second-generation AEDs used as monotherapy were compared with placebo or other AEDs: oxcarbazepine, felbamate, lamotrigine, gabapentin, levetiracetam, pregabalin, zonisamide, topiramate, and tiagabine. Vigabatrin has only been registered as monotherapy for West syndrome and has limited use in other epilepsies due to its irreversible side effect of visual loss. Therefore, it was not included in this review. Studies were identified using PubMed (Medline), Embase and the Cochrane Library (from January 1990 until January 2010). The following search terms were used: 'epilepsy AND child* AND monotherapy AND (oxcarbazepine OR felbamate OR lamotrigine OR gabapentin OR levetiracetam OR pregabalin OR zonisamide OR topiramate OR tiagabine)' with the limitation: Randomized Controlled Trials (RCT). The obtained studies were used to search for further references. References in English, German, French, Spanish, Italian, and Dutch were included.

If a study included both children and adults, it was reviewed only if the results of efficacy and safety were reported separately for children. Of these studies only the data concerning children are described and discussed. All reports were assessed for study design and methodological quality for which we evaluated the method of randomization concealment, duration of treatment and follow-up, attrition and whether children had been excluded from the analyses. We abstracted clinical characteristics of participants and data on seizure-freedom, retention rate, time to treatment failure, >50% seizure-reduction, and reported adverse events. The data were independently extracted from the trial reports by two authors (AW and PC). If retention rate was not given in the article, it was calculated by us. Since this systemic review includes reports on a series of AEDs evaluated in children with various different epilepsy syndromes, we chose to perform a descriptive analysis without pooling of data.

RESULTS AND DISCUSSION

In total, 32 studies were identified with our literature search. Eight of these studies specifically reported data of patients under the age of 18 years.[1, 2, 4-9] The most important reasons that the other 22 studies did not meet our inclusion criteria were that they did not report data on children separately (n=11)[12-22] or they concerned add-on treatment instead of monotherapy (n=6).[23-28] The remaining studies were not included because the second-generation AED was not compared with another AED (n=3)[29-31], it did not include children at all (n=1)[32], the primary endpoint was the effect on cognitive function (n=1)[33], it was written in Chinese (n=1)[34], or it concerned a review (n=1).[35] One additional study was included that was only published as an abstract.[3] Consequently, nine studies are discussed in this review.

Design and methodological quality

Study details are summarized in Table 2. Three studies had a placebo-controlled design.[1, 3, 4] The response of placebo can be subtracted from the response of the tested AED in order to get the true response of the tested drug. In the other studies a second-generation AED was compared with one or more other AEDs.[2, 5-9]

Most studies in this review included children with one specific type of newly diagnosed epilepsy: absence epilepsy, BECTS or partial epilepsy.[1, 3-7, 9] An advantage of including one epilepsy syndrome is that the tested drug can be compared with the first-choice treatment for that specific epilepsy syndrome. Whether the results can be extrapolated to other epilepsy syndromes is, however, unknown with this type of design. Some AEDs are known to be efficacious in certain epilepsy syndromes while they may exacerbate some seizure types in other epilepsy syndromes. Efficacy and safety of AEDs need, therefore, to be determined in children with different epilepsy syndromes separately.

Overall, five studies used a double-blind study design and four an open-label design. A double-blind design gives the most valid estimation of efficacy and safety. The follow-up period of the studies varied between two weeks and 24 months. In general, the follow-up period of the open label studies was longer (mean 57 weeks, range 18 weeks–24 months) than that of the double-blind studies (mean 23 weeks, range 2–48 weeks). Two of the three placebo-controlled studies had a follow-up period of less than one month because it is strongly disputable to treat children with epilepsy with a placebo drug for a long duration.[1, 4]

Most studies were multi-centered, giving the opportunity to evaluate a larger number of children.[1-5, 8, 9] Especially in trials on efficacy and safety of drugs, a multi-center study design is needed to obtain sufficient power to draw any conclusions. Only three studies described their power calculation well[1, 2, 4], of which one already indicated that their study had only 50% power to detect a treatment difference with at least 50% reduction in seizure frequency.[1] The power of some of the other studies might also have been too low to detect significant differences in their primary outcome between treatments. Two studies clearly described the procedure of randomization and

blinding.[2, 8] A meta-analysis of 255 obstetric trials has shown that trials with inadequate reporting of randomization and blinding overestimated the treatment effect by 30% compared with trials in which this information was given.[36] The possibility exists that this bias has also occurred in the studies described in this review. Five studies did not analyze efficacy using intention-to-treat analyses.[1-4, 9] This might lead to an overestimation of the true treatment effect. For example, Guerreiro et al. analyzed efficacy in the group that ended the study instead of in the group that entered the study, giving rise to a potential selection bias.[2] Patients who have been withdrawn from the study (for any reason) should also be included in the analyses.

None of the studies reported to have installed a Data Safety Monitoring Committee (DSMC). Such a committee consists of a group of independent experts external to a study critically assessing the progress and safety and efficacy outcome data (unblinded if necessary) of a clinical study.[37, 38]

To summarize, the study design used in many of the available studies on efficacy and safety of AEDs impair valid conclusions. To study efficacy and safety of a drug requires a double-blind, parallel group, multi-center design with adequate power in order to obtain valid, useful and unbiased results. For each epilepsy syndrome, efficacy and safety of AEDs need to be determined separately. Randomization procedures should be elucidated, power calculations should be made, and statistically correct analyses of the results must be performed. None of the included studies showed all these characteristics. Finally, a DSMC should be installed, if appropriate, to monitor progress, safety, integrity and design aspects of the study.

Medication and dosage

At least four studies were performed before the tested AED was registered as monotherapy.[1-4] All these studies were sponsored by industry. In such cases a publication bias might occur, because industry might be more eager to get statistically significant results in favor of their product published. We performed no explicit search for unpublished trials. No differences in outcome were, however, observed between the published studies that were sponsored by the industry[1-5, 8] and those that were not sponsored.[6, 7, 9]

Guerreiro et al. used phenytoin as control treatment, whereas phenytoin is not a first choice treatment for children with partial epilepsy.[2] This led to biased results in favor of oxcarbazepine. If there is no consensus in treatment for a specific epilepsy syndrome it is hard to prescribe only one predefined drug. In the study of Wheless et al., the investigator was, therefore, allowed to make an individual choice for every child between carbamazepine and valproic acid based on the clinical presentation, with a fixed dose-schedule for each drug.[8] The dosage of the tested second-generation AEDs varied between studies (Table 2), making efficacy comparisons difficult. For example, the dose of gabapentin was 15-20 mg/kg/day in the study of Trudeau et al. versus 30 mg/kg/day in the study of Bourgeois et al.[1, 3] Furthermore, the study of Wheless et al. used a dose of 100 mg/day topiramate in one group, whereas the effective dose range for topiramate monotherapy is 100 to 400 mg/day.[8, 39] The used dosages in the studies of Trudeau et al. and Wheless et al. could have been subtherapeutic, leading to biased results. One study defined a titration schedule of the

Table 2. Controlled monotherapy studies on new antiepileptic drugs in children with epilepsy

Study	Study design	Age (yrs)	Epilepsy syndrome	Intervention and comparison	N randomized (N analyzed)	Study duration (weeks)
Trudeau et al. (1996)	DB, PC, MC	4 – 12	ND absence epilepsy	GBP 15-20mg/kg/day Placebo	15 (14) 18 (17)	2
Bourgeois et al. (1998)	DB, PC, MC	4 – 13	BECTS	GBP 30mg/kg/day Placebo	113 (106) 112 (106)	36
Frank et al. (1999)	DB, PC, MC	3 – 15	ND absence epilepsy, SF on LTG	LTG 1-15mg/kg/day Placebo	15 (14) 14 (14)	4
Nieto-Barrera et al. (2001)	OL, PG, MC	2 – 12	ND partial epilepsy	LTG 2-15mg/kg/day CBZ 5-40 mg/kg/day	158 75	18
Coppola et al. (2004)	OL, PG	3 – 13	ND absence epilepsy	LTG 1-12mg/kg/day VPA 10-30 mg/kg/day	19 19	52
Wheless et al. (2004)	DB, PG, MC	6 –16	ND epilepsy	TPM 100-200mg/day CBZ 600mg/day VPA 1250mg/day	77 23 19	≤100 (mean 40)
Resendiz-Aparicio et al. (2004)	OL, PG, MC	2 – 18	ND partial epilepsy	TPM 1-9mg/kg/day CBZ 20-25mg/kg/day	46 (33) 42 (32)	52
Guerreiro et al. (1997)	DB, PG, MC	5 – 18	ND PE or GTCS	OXC 450-2400mg/day PHT 150-800mg/day	97 (81) 96 (77)	48
Coppola et al. (2007)	OL, PG	3 – 14	ND BECTS	LEV 20-30mg/kg/day OXC 20-35mg/kg/day	21 18	52-104 (mean 80)

BECTS, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; DB, double blind; GBP, gabapentin; GTCS, generalized tonic-clonic seizures; LEV, levetiracetam; LTG, lamotrigine; MC, multi center; N, number; ND, newly diagnosed; OL, open label; OXC, oxcarbazepine; PC, placebo-controlled; PE, partial epilepsy; PG, parallel group; PHT, phenytoin; SF, seizure-free; TPM, topiramate; VPA, valproic acid; yrs, years.

tested second-generation AED but not of the control first-generation AED[5], and some studies used a fixed dose design in contrast to an individual dose design, which may have led to subtherapeutic doses in some patients.[2, 8] Especially in children, the administered dosages of the AED should be based on bodyweight and be prescribed in mg/kg/day. Coppola et al. used a slow, usual, titration phase for lamotrigine, and compared efficacy between valproic acid and lamotrigine already during this period, leading to a significantly lower percentage of patients being seizure-free in the lamotrigine group during the first weeks.[6] These differences were not observed after longer follow-up. Comparisons should, therefore, only be made after the titration phase and when all patients are treated with optimal therapeutic dosages.

All but one of the studies only included children that had not yet been treated with AEDs or other treatments for their epilepsy, with the exception of acute treatment of a seizure. In the study of Frank et al. all children with absence epilepsy received lamotrigine.[4] Only children who became seizure-free on a maximum dosage of lamotrigine were randomized (continuation of lamotrigine or change to placebo). Eleven of the 45 children were excluded for randomization because they did not become seizure-free on lamotrigine, giving a selection bias in favor of lamotrigine. Another problem of this study was that safety could not be compared between the lamotrigine and 'placebo' group, because all children received lamotrigine before randomization.

To summarize, the substandard treatment regimens used in most of the available studies on efficacy and safety of AEDs impair valid conclusions. Optimal treatment regimens must be used, with a first choice AED in the control group and optimal therapeutic dosages in both groups. Furthermore, the tested drugs should only be compared in the period during which the AEDs are given in the optimal therapeutic dosages and not during the titration phase. Only then, a good comparison can be made between the tested and the control AED.

Outcome measures, efficacy, safety

The aim of all studies was to investigate the efficacy and safety of monotherapy with second-generation AEDs in children and to demonstrate that second-generation AEDs are as effective as or even better than first-generation AEDs and have less adverse events.

The used primary outcome measures in the described studies were: being seizure-free at a certain moment during follow-up[2, 4-7], change in seizure frequency[1, 9], or time to treatment failure event (i.e. duration of treatment, in which all reasons of dropping out, such as no efficacy or adverse events, are included; also named time to exit).[3, 8] In the three studies that examined children with absence epilepsy, 'seizure-free' status was determined objectively mainly by a hyperventilation provocation EEG.[1, 4, 6] This epilepsy syndrome has the advantage of specific EEG changes during hyperventilation and an EEG can, therefore, be used as an early objective measurement. For other epilepsy syndromes a long follow-up period is important to obtain valuable results of the efficacy of the tested drug. Seizure frequency may be low in some patients, and with a short follow-up period these patients appear to be seizure-free which may not be the case.

Efficacy and safety results of all nine studies are listed in Table 3. They appear to show similar efficacy and safety of first- and second-generation AEDs in children. Only one study demonstrated a significantly higher efficacy of a second-generation AED (lamotrigine versus placebo in children with absence epilepsy).[4] One of the studies with topiramate showed a better efficacy of topiramate than of carbamazepine in children with partial epilepsy after six and nine months (mean 1 and 0 seizures/month versus mean 4 and 5 seizures/months, respectively, no confidence intervals given, $p = 0.01$), but not after twelve months.[9] In one of the six studies comparing a second-generation AED to another AED significantly less patients dropped out after the second generation AED (oxcarbazepine 2% versus phenytoin 19%, $p = 0.002$).[2] Adverse events were also more often reported after lamotrigine than after valproic acid in children with absence epilepsy, but no adverse effect sizes or *p*-values were provided in this study (Table 3).[6] The frequency of the occurring adverse events was not compared between the two AED treatments in some studies.[2, 6, 9] In all studies only spontaneously reported adverse events were taken into account. None of them used a standardized questionnaire of which the utilization has been shown to lead to higher percentages of patients reporting adverse events.[40-42] It is possible that certain complaints are mentioned more often if specifically asked than if they have to be reported spontaneously. To be able to compare the percentage of reported adverse events and to prevent a selective outcome reporting bias, it would be ideal to use a standardized side effects questionnaire in each study on safety of an AED. This questionnaire should contain questions covering physical function, emotional well-being, cognitive function, and behavior. To be able to study and understand these adverse events, they have to be studied prospectively, i.e. the questionnaire should also be completed before the start of the investigational drug. Cognitive and behavioral side effects may also be objectified by performing neuropsychological investigations before the start of the investigational drug and at the end of the trial. Furthermore, correlations should be made between the occurrence of adverse events and change in seizure frequency during treatment.

The choice whether the occurrence of a certain non-life threatening adverse event is acceptable or that the AED has to be discontinued because of this adverse event is personal. For that reason, the primary outcome was time to treatment failure in two studies.[3, 8] Efficacy and safety are linked in this parameter and it, therefore, presents all reasons leading to treatment failure. In one of these studies, no fixed treatment period was used, however, which may give a false reflection of time to treatment failure since patients who were followed for six months will by definition have a shorter time to exit than patients followed for 20 months.[8]

Another outcome parameter that combines efficacy and safety is retention rate, i.e. the percentage of the population still using the tested AED at a certain time point. In several studies the retention rate was given[1-3, 5, 6, 8], for the remaining studies the retention rate was calculated by us (Table 3).[4, 7, 9] A difference in retention rate of more than 10% between the tested AEDs was observed in the studies of Bourgeois et al. and Coppola et al.[3, 6, 7] Most drop-outs were caused by lack of efficacy in these studies. Retention rate combines all reasons for withdrawal of a certain AED, and gives, therefore, a true indication of what occurs in practice as well.

Summarized, the follow-up period and primary outcomes in most of the available studies on efficacy and safety of AEDs are substandard. To be able to draw valid conclusions, the follow-up period should be fixed and long enough. An appropriate primary outcome is time to treatment failure and/or retention rate in order to get a good reflection of both efficacy and safety. If outcomes are uniform across clinical trials, the results are easier to interpret and compare, which reduces the risk of outcome reporting bias. Furthermore, use of standardized side effects questionnaires should be considered.

CONCLUSIONS AND RECOMMENDATIONS

Based on the available controlled trials, the tested second-generation AEDs seem equally effective as first-generation AEDs and do not give fewer side-effects. In most studies, however, the methodological quality was inadequate. Considerable heterogeneity in study design, inclusion criteria and primary endpoints impairs a useful comparison of studies and drawing of sound conclusions. No inference on equivalence or superiority, whether in efficacy or safety, can be based on these studies. Better randomized controlled studies are needed in this field. There are several challenges in creating a satisfying study design for monotherapy studies evaluating the efficacy and safety of second-generation AEDs in children with epilepsy. An important proportion of children will become seizure-free due to the natural history of their epilepsy syndrome, so it is hard to know what exactly the efficacy of the administered drug is in uncontrolled studies. This problem is largely solved using a randomized controlled study design. Furthermore, because good seizure control is very important, it is generally considered unethical to compare the tested drug with placebo treatment. Last of all, since pharmacokinetics may be different in children compared to adults, it may be difficult to determine the best titration period and dosage-schedule for children, even when safety has been proved. We give some recommendations for trial design from which future studies may benefit and which lead to minimization of the likelihood of bias.

First, a randomized double-blind, parallel group study is preferable because of objectiveness. Second, multi-center studies make it possible to analyze more patients leading to sufficient sample sizes. Third, power calculations have to be performed in order to include enough patients. Fourth, the follow-up period of the study has to be fixed and long enough (at least one year) to be able to draw any conclusions; Perucca and Tomson even suggest a follow-up period of at least three years.[43] Fifth, epilepsy seizures and syndromes must be classified with objective measurements, like the criteria of the International League Against Epilepsy, and efficacy should be determined in specific seizures and syndromes.[44, 45] Sixth, the tested second-generation AED must be given in an optimal dose with a regular titration schedule and the control group must be treated with a first-choice AED in an optimal dose and titration schedule as well. The analysis of efficacy should be based on the period when the optimal dose is used. Seventh, the efficacy and safety of the tested AED can best be measured as time to treatment failure or retention rate, while these parameters combine efficacy and safety, and standardized side effects questionnaires should be used. Last of all, during the planning phase of a clinical trial the need for a Data Safety Monitoring Committee should be assessed.

In the Netherlands, as well as in some other countries in Europe and other continents, a pediatric drug research network has recently been set up to improve the speed, quality and integration of clinical drug research in children (www.mcrn.nl). The most important aim of this network is to establish the evidence base for new and existing drugs that are both safe and effective for children, in order to ameliorate patient care.

Table 3. Efficacy and safety of new antiepileptic drugs in controlled monotherapy studies in children with epilepsy

Article	Seizure-free (%)	Retention (%)	Other efficacy parameters	Withdrawal due to AE (%)	Most common AE (%)[d]
Trudeau et al. (1996)	n.i.	GBP 100 PBO 100	>50% seizure-red: GBP 7%, PBO 24% , Seizure frequency change NS	0	GBP: somnolence (≥14), dizziness (≥14)
Bourgeois et al. (1998)	n.i.	GBP 57 PBO 44	TFE GBP > PBO[a]	GBP 4 PBO 0	n.i.
Frank et al. (1999)	LTG 60[b] PBO 21	LTG 93 PBO 100		0	LTG: rash (22), abdominal pain (11)
Nieto-Barrera et al. (2001)	LTG 56[a] CBZ 64	LTG 87 CBZ 85		LTG 5 CBZ 7	LTG: infection (13) CBZ: headache (16), dizziness (15), pharyngitis (11)
Coppola et al. (2004)	LTG 53[a] VPA 68	LTG 68 VPA 84		0	LTG: headache (11)
Wheless et al. (2004)	TPM100 63 TPM200 59 CBZ 39 VPA 53	Overall 54	TFE: TPM100 307D[a] TPM200 291D CBZ 268D VPA 227D	TPM100 11 TPM200 18 CBZ 4 VPA 32	TPM100: headache (37), fatigue (16), appetite loss (16) TPM200: fatigue (26) CBZ: headache (22), fatigue (17), dizziness (17), nausea (17) VPA: somnolence (32), fatigue (21), weight gain (21), headache (16)
Resendiz-Aparicio et al. (2004)	TPM 65[a] CBZ 62	TPM 72 CBZ 76	>50% seizure-red: TPM 70% CBZ 64%	TPM 2 CBZ 2	 CBZ: somnolence (19)
Guerreiro et al. (1997)	OXC 60[a] PHT 60	OXC 75 PHT 65	Seizure freq/W: OXC 0.07 PHT 0.04	OXC 2[c] PHT 19	OXC: somnolence (25) PHT: somnolence (30), gum hyperplasia (26), dizziness (22)
Coppola et al. (2007)	LEV 90[a] OXC 72	LEV 86 OXC 67		LEV 5 OXC 6	

[a] Not significantly different
[b] $p<0.05$
[c] $p<0.01$
[d] only adverse events that were reported by more than 10% of the subjects are mentioned (for the studies of Wheless and Guerreiro if reported by more than 15%)
AE, adverse events; CBZ, carbamazepine; D, days; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; n.i., not indicated; NS, not significant; OXC, oxcarbazepine; PBO, placebo; PHT, phenytoin; Seizure freq/W, seizure frequency per week; seizure-red, seizure reduction; TFE, time to treatment failure; TPM, topiramate (100 = 100mg/day, 200 = 200mg/day); VPA, valproic acid.

REFERENCES

1. Trudeau V, Myers S, LaMoreaux L, et al. Gabapentin in naive childhood absence epilepsy: results from two double-blind, placebo-controlled, multicenter studies. J Child Neurol 1996;11:470-475.
2. Guerreiro MM, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res 1997;27:205-213.
3. Bourgeois B, Brown LW, Pellock JM, et al. Gabapentin (neurontin) monotherapy in children with benign childhood epilepsy with centrotemporal spikes (BECTS): a 36-week, double-blind, placebo-controlled study. Epilepsia 1998;39 (Suppl. 6):163.
4. Frank LM, Enlow T, Holmes GL, et al. Lamictal (lamotrigine) monotherapy for typical absence seizures in children. Epilepsia 1999;40:973-979.
5. Nieto-Barrera M, Brozmanova M, Capovilla G, et al. A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy. Epilepsy Res 2001;46:145-155.
6. Coppola G, Auricchio G, Federico R, et al. Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. Epilepsia 2004;45:1049-1053.
7. Coppola G, Franzoni E, Verrotti A, et al. Levetiracetam or oxcarbazepine as monotherapy in newly diagnosed benign epilepsy of childhood with centrotemporal spikes (BECTS): An open-label, parallel group trial. Brain Dev 2007;29:281-284.
8. Wheless JW, Neto W, Wang S, et al. Topiramate, carbamazepine, and valproate monotherapy: double-blind comparison in children with newly diagnosed epilepsy. J Child Neurol 2004;19:135-141.
9. Resendiz-Aparicio JC, Rodriguez-Rodriguez E, Contreras-Bernal J, et al. A randomised open trial comparing monotherapy with topiramate versus carbamazepine in the treatment of paediatric patients with recently diagnosed epilepsy. Rev Neurol 2004;39:201-204.
10. Dulac O. Issues in paediatric epilepsy. Acta Neurol Scand Suppl 2005;182:9-11.
11. Chung AM and Eiland LS. Use of second-generation antiepileptic drugs in the pediatric population. Paediatr Drugs 2008;10:217-254.
12. Chadwick DW, Anhut H, Greiner MJ, et al. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. international gabapentin monotherapy study group 945-77. Neurology 1998;51:1282-1288.
13. Schachter SC, Vazquez B, Fisher RS, et al. Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures. Neurology 1999;52:732-737.
14. Ingwersen SH, Pedersen PC, Groes L, et al. Population pharmacokinetics of tiagabine in epileptic patients on monotherapy. Eur J Pharm Sci 2000;11:247-254.
15. Beydoun A, Sachdeo RC, Rosenfeld WE, et al. Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. Neurology 2000;54:2245-2251.
16. Sachdeo R, Beydoun A, Schachter S, et al. Oxcarbazepine (trileptal) as monotherapy in patients with partial seizures. Neurology 2001;57:864-871.
17. Biton V, Mirza W, Montouris G, et al. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. Neurology 2001;56:172-177.
18. Beydoun A, Sachdeo RC, Kutluay E, et al. Sustained efficacy and long-term safety of oxcarbazepine: one-year open-label extension of a study in refractory partial epilepsy. Epilepsia 2003;44:1160-1165.
19. Biton V, Levisohn P, Hoyler S, et al. Lamotrigine versus valproate monotherapy-associated weight change in adolescents with epilepsy: Results from a post hoc analysis of a randomized, double-blind clinical trial. J Child Neurol 2003;18:133-139.
20. Privitera MD, Brodie MJ, Mattson RH, et al. Topiramate, carbamazepine and valproate monotherapy: double-blind comparison in newly diagnosed epilepsy. Acta Neurol Scand 2003;107:165-175.
21. Gilliam FG, Veloso F, Bomhof MA, et al. A dose-comparison trial of topiramate as monotherapy in recently diagnosed partial epilepsy. Neurology 2003;60:196-202.

22. Arroyo S, Dodson WE, Privitera MD, et al. Randomized dose-controlled study of topiramate as first-line therapy in epilepsy. Acta Neurol Scand 2005;112:214-222.
23. Duchowny M, Pellock JM, Graf WD, et al. A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children. Neurology 1999;53:1724-1731.
24. Siegel H, Kelley K, Stertz B, et al. The efficacy of felbamate as add-on therapy to valproic acid in the Lennox-Gastaut Syndrome. Epilepsy Res 1999;34:91-97.
25. Lindberger M, Alenius M, Frisen L, et al. Gabapentin versus vigabatrin as first add-on for patients with partial seizures that failed to respond to monotherapy: a randomized, double-blind, dose titration study. Epilepsia 2000;41:1289-1295.
26. Glauser TA, Nigro M, Sachdeo R, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures. Neurology 2000;54:2237-2244.
27. Sethi A, Chandra D, Puri V, et al. Gabapentin and lamotrigine in Indian patients of partial epilepsy refractory to carbamazepine. Neurol India 2002;50:359-363.
28. Noachtar S, Andermann E, Meyvisch P, et al. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. Neurology 2008;70:607-616.
29. Glauser TA, Dlugos DJ, Dodson WE, et al. Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents. J Child Neurol 2007;22:693-699.
30. Verrotti A, Cerminara C, Domizio S, et al. Levetiracetam in absence epilepsy. Dev Med Child Neurol 2008;50:850-853.
31. Sankar R, Ramsay E, McKay A, et al. A multicenter, outpatient, open-label study to evaluate the dosing, effectiveness, and safety of topiramate as monotherapy in the treatment of epilepsy in clinical practice. Epilepsy Behav 2009;15:506-512.
32. Aikia M, Jutila L, Salmenpera T, et al. Comparison of the cognitive effects of tiagabine and carbamazepine as monotherapy in newly diagnosed adult patients with partial epilepsy: pooled analysis of two long-term, randomized, follow-up studies. Epilepsia 2006;47:1121-1127.
33. Kang HC, Eun BL, Wu Lee C, et al. The effects on cognitive function and behavioral problems of topiramate compared to carbamazepine as monotherapy for children with benign rolandic epilepsy. Epilepsia 2007;48:1716-1723.
34. Huang TS, Zhu JL, Li B, et al. Valproic acid versus lamotrigine as a monotherapy for absence epilepsy in children. Zhongguo Dang Dai Er Ke Za Zhi 2009;11:653-655.
35. Jensen PK. Felbamate in the treatment of refractory partial-onset seizures. Epilepsia 1993;34 Suppl 7:S25-9.
36. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-412.
37. European Medicines Agency. Guideline on Data Monitoring Committees. https://www.ema.europa.eu/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf.
38. Fernandes RM, van der Lee JH, Offringa M. A systematic review of the reporting of data monitoring committees' roles, interim analysis and early termination in pediatric clinical trials. BMC Pediatr 2009;9:77-2431-9-77.
39. Arroyo S, Squires L, Wang S, et al. Topiramate: effective as monotherapy in dose--response study in newly-diagnosed epilepsy. Epilepsia 2002;43 (Suppl.7):241.
40. Carpay JA, Aldenkamp AP, van Donselaar CA. Complaints associated with the use of antiepileptic drugs: results from a community-based study. Seizure 2005;14:198-206.
41. Uijl SG, Uiterwaal CS, Aldenkamp AP, et al. A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs. Seizure 2006;15:242-248.
42. Callenbach PM, Arts WF, ten Houten R, et al. Add-on levetiracetam in children and adolescents with refractory epilepsy: results of an open-label multi-centre study. Eur J Paediatr Neurol 2008;12:321-327.
43. Perucca E and Tomson T. Monotherapy trials with the new antiepileptic drugs: Study designs, practical relevance and ethical implications. Epilepsy Res 1999;33:247-262.

44. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489-501.
45. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-399.

CHAPTER 3

Antiepileptic drug prescription in Dutch children from 2006-2014 using pharmacy-dispensing data

A. Weijenberg, H.J. Bos, C.C.M. Schuiling-Veninga, O.F. Brouwer, P.M. C. Callenbach

Epilepsy Research 2018;146:21-27

ABSTRACT

Objective

In the last two decades several new antiepileptic drugs (AEDs) have become available. The aim of our study was to analyze whether and how AED prescribing patterns in Dutch children have changed during the last decade and whether these changes were supported by guidelines and results from recently available trials.

Methods

From a large community pharmacy-dispensing database in the Netherlands, we identified children aged 0–19 years who received at least one prescription for an AED between 2006 and 2014. Children who also received prescriptions for migraine or psychiatric disorders were excluded. We calculated year-prevalences and -incidences of AED use with emphasis on old versus new AEDs, and individual AEDs. We evaluated these results, including the course of AED prescribing.

Results

During the study period, the prescribing prevalence of old AEDs decreased from 1.61 per 1000 (95% C.I. 1.40–1.82) to 1.39 per 1000 (95% C.I. 1.18–1.60); for new AEDs it increased from 0.58 per 1000 (95% C.I. 0.45–0.71) to 1.35 per 1000 (95% C.I. 1.14–1.56). Valproic acid was the most frequently initiated AED in 2006. From 2010, prescribing of old and new AEDs became equal with levetiracetam as the most often initiated AED since 2012. This drug was recommended for all seizure types in the 2013 Dutch national epilepsy guideline. Only 5.5% of the children used AED combination therapy. Of those on monotherapy, 85.7% remained on the first prescribed AED.

Conclusions

In the last 10 years, prescribing of new AEDs increased at the expense of old AEDs. Levetiracetam has replaced valproic acid as the most frequently prescribed first line antiepileptic drug in children since 2012, which is in line with national guidelines.

INTRODUCTION

Epilepsy is one of the most common neurological disorders in childhood, with a median incidence of 82/100,000 in children and with antiepileptic drugs (AEDs) being first choice treatment.[1] During the last 25 years many new, so called second- and third-generation, AEDs have become available (Table 1).[2]

Table 1. Antiepileptic drugs in the Netherlands

AED	Registration for children[a] in the Netherlands in 2018[b] (age; mono/add-on)	Year of registration in children[a] in Europe
Old		
Carbamazepine	all	n.d.
Clobazam	all	n.d.
Clonazepam	all	n.d.
Ethosuximide	all	n.d.
Phenobarbital	all	n.d.
Phenytoin	all	n.d.
Primidone	all	n.d.
Sulthiame	n.a.	n.a.
Valproic Acid	all	n.d.
New		
Felbamate	≥4 years: add-on	1995
Gabapentin	≥12 years: mono ≥6 years: add-on	2007
Lacosamide	≥4 years mono and add-on	2017
Lamotrigine	≥12 years: mono ≥2 years: add-on	2000
Levetiracetam	>16 years: mono >1 month: add-on	2005
Oxcarbazepine	≥6 years mono and add-on	2000
Perampanel	≥12 years: add-on	2012
Pregabalin	n.a.	n.a.
Retigabine	n.a.	n.a
Rufinamide	≥4 years: add-on	2007
Stiripentol	all add-on	2007
Topiramate	≥6 years: mono ≥2 years: mono absence epilepsy ≥2 years: add-on	1999
Vigabatrin	West syndrome: mono all add-on	1998
Zonisamide	≥6 years: add-on	2013

[a] children <16 years of age
[b] College ter beoordeling van geneesmiddelen (2018)
AED, antiepileptic drug; n.a., not approved in the Netherlands; n.d., not documented

For most of them, no data from randomized controlled trials (RCTs) are available for children, especially not for AED monotherapy.[3] As a consequence, most of these new AEDs are only registered as add-on treatment for specific seizure types, and are prescribed off-label as monotherapy in children, not supported by evidence-based guidelines but based on the doctor's personal preference. Little is known about these individual and personal prescribing patterns and changes over time. Van de Vrie-Hoekstra et al. described utilization of AEDs of children in the Netherlands

from 1997 to 2005.[4] Nine more studies have been published about prescribing patterns of AEDs in children, most of them describing cohorts before 2010.[5-13] They all concluded that old AEDs (valproic acid, carbamazepine, phenytoin, phenobarbital) were most commonly prescribed, but that the proportion of prescribing new AEDs (lamotrigine, levetiracetam, topiramate, oxcarbazepine) was increasing considerably over time. Since 2010 new AEDs have become more established, more of them have become available, including liquid formulations for some, and new clinical trials and guidelines have been published.[14-17]

The aim of our study was to describe and analyze prescribing patterns of AEDs in children from 2006 to 2014. Furthermore, factors that may have influenced prescribing patterns are discussed, such as results of new RCTs, updates of (inter)national guidelines, off-label prescribing, costs, and/or personal experience of the prescribing doctors.

MATERIAL AND METHODS

This study is an extension of an earlier study performed in our center, and we used the same methodological principles.[4] Information on drug use was extracted from the IADB.nl database.[18] This database contains pharmacy-dispensing data of more than 600,000 persons from more than 50 Dutch community pharmacies located in different parts of The Netherlands, and is proven to be representative for the Netherlands with respect to age distribution and prevalence of drugs used.[18] Community pharmacies contain an almost complete history of prescribed drugs because Dutch patients usually are registered at a single pharmacy. The IADB.nl database anonymously provides per patient, among other data, the information on drug use, like the dispensed drug represented in the Anatomical Therapeutical Chemical (ATC) classification, number of days the drug was prescribed, dispensing date, and the number of defined daily doses based on the definition by the WHO.[19] In-hospital prescriptions and the use of over-the-counter drugs are not included in the database, but AEDs are non-over-the-counter drugs. Because data are stored anonymously and this database does not fall under the scope of the Medical Research Involving Human Subjects Act, approval of the medical ethics committee was not required.

Study population

Children aged 0–19 years who received at least one prescription for an AED between 2006 and 2014 were selected from the IADB.nl. All AEDs (ATC-group N03A) available in the Netherlands were included, regardless whether they were registered for children. Furthermore, clobazam (ATC-code N05BA09) was included if used together with another AED, since this combination of drugs can be used for chronic treatment in children with epilepsy.

The IADB.nl provides information on drug use, without specification of the diagnosis. Since some AEDs are also prescribed for migraine or psychiatric disorders, we excluded children who were more likely to have migraine or a psychiatric disorder; i.e. children who received at least two or more prescriptions of propranolol and/or anti-migraine drugs (ATC-code N02C* or N07CA03), or received more than one prescription for an anti-depressant (ATC-code N06A*), or received more than one prescription for anti-psychotics (ATC-code N05A*) between 2006 and 2014. In the former Dutch study that used the same exclusion criteria, children who were more likely to have migraine or a psychiatric disorder were not excluded.[4] In their study it was estimated that AEDs had been prescribed for epilepsy in at least 80% of the included children, while approximately 10% had received the drugs for mood disorders and 5% for migraine.

Data analysis

Prevalences and incidences of the use of all AEDs together were calculated per year over a period of 9 years from 2006 to 2014. AEDs were then stratified by type as old or new AED (Table 1) and prevalences and incidences were calculated, including 95% confidence intervals. Finally, prevalences and incidences were calculated for each individual AED. If no overlap between confidence intervals was observed, prescribing of AEDs was considered significantly different.

Annual prevalences were defined as the number of children receiving at least one prescription for an AED divided by the total number of children in the population (per sex and age category) in the respective years, and then multiplied by 1000.

The cumulative incidence of AED prescriptions was based on the number of children who received an initial prescription for a certain AED per year. Every child could be an initial user once, but when a child had two prescriptions for different AEDs as initial treatment, both AEDs were counted. To identify initial users, children had to be in the database at least 6 months before initial treatment with an AED started or were aged ≤ 2 years.

To evaluate the course of AED prescribing, children with a known start date and end date of therapy with AEDs were included as well as children having a running prescription at the end of the study period (31st of December 2014). The start of the therapy was defined the same way as for cumulative incidences. The theoretical end date of the treatment was calculated by dividing the prescribed number of tablets of the last prescription by the daily dosage. The therapy was defined as being ended if there were 90 days or more without AEDs after the theoretical end date of drug use. To be able to assess ending of AED use, children had to be in the IADB.nl for at least 90 days or more after the theoretical end date, otherwise they were excluded (except for children with a running prescription on 31st of December 2014). For each child, the start date and theoretical end date of each prescribed AED was calculated and, afterwards, children were divided in two groups: monotherapy or combination therapy. Combination therapy was defined as a prescription for two or more AEDs at the same time with an overlap of at least 90 days. Restart was defined as start after a discontinuation of AED treatment of at least 90 days. For all children, the course of AED prescriptions was evaluated.

Furthermore, the course of AED prescribing in our cohort was compared with national guidelines and results from available trials.

RESULTS

From the IADB.nl, 2450 children were identified who received at least one prescription for an AED between 2006 and 2014. Of these 2450 children, 1280 (52.2%) were boys. Of the 2450 children 966 were excluded: 219 (9%) were supposed to have migraine, 720 (29%) were supposed to have a psychiatric problem and 27 (1%) only used clobazam without another AED. Most of the children more likely to have migraine because they used propranolol and/or triptans, also used valproic acid and/or topiramate. Valproic acid was also one of the most often prescribed AED in children who most likely had a psychiatric disorder. Of the children considered to have a psychiatric problem, the minority used an anti-depressant (ATC code N06A*), amitriptyline being most prescribed, followed by selective serotonin reuptake inhibitors (SSRIs). The majority used an anti-psychotic drug (N05A*), or a combination of an anti-psychotic drug and an anti-depressant. Amitriptylin was often combined with pregabalin or gabapentin which suggests a diagnosis of neuropathic pain, whereas in combination with AEDs it is also prescribed for the treatment of chronic headache. Eventually, 1484 children were included in our study.

The estimated population of children covered by the IADB.nl per year, the annual prevalence, and cumulative incidence of AED use among these children are shown in Table 2. The overall prevalence and incidence remained constant and there were no differences between sexes.

Table 2. Population of the IADB.nl, prevalence and incidence of AED use per 1000 children (0 - 19 years)

Year	Total number of children	Prevalence	95% Confidence interval	% male	Incidence	95% Confidence interval	% male
2006	135,428	1.99	1.76 – 2.23	53	0.50	0.38 – 0.62	51
2007	135,745	2.11	1.87 – 2.36	53	0.63	0.50 – 0.77	60
2008	134,328	1.95	1.71 – 2.19	51	0.52	0.40 – 0.64	51
2009	136,444	2.44	2.18 – 2.70	54	0.79	0.64 – 0.94	59
2010	138,212	2.17	1.92 – 2.41	57	0.55	0.43 – 0.67	54
2011	135,410	2.45	2.19 – 2.71	52	0.89	0.73 – 1.05	47
2012	133,447	2.44	2.18 – 2.71	57	0.87	0.72 – 1.03	55
2013	130,458	2.40	2.14 – 2.67	52	0.83	0.67 – 0.98	47
2014	119,707[a]	2.32	2.05 – 2.59	52	0.68	0.53 – 0.82	55

[a] decrease in population because of drop-out of one pharmacist

Prescription of old versus new AEDs

Figure 1 shows the overall annual prevalence of AED use, which varied from 1.95 to 2.45 per 1,000 children, as well as the prevalence by type of AED (old versus new). Since clonazepam belongs to ATC-group NO3A (old AED), clonazepam is also included in Figure 1. From 2006 to 2011, old AEDs were significantly more often used than new AEDs as shown by the confidence intervals, but the use of new AEDs increased over the years at the expense of old AEDs. From 2012 onwards the prevalence of old and new AED use was identical.

Prescription of individual AEDs

All AEDs of ATC-group N03A were prescribed at some time to children in the IADB.nl database,

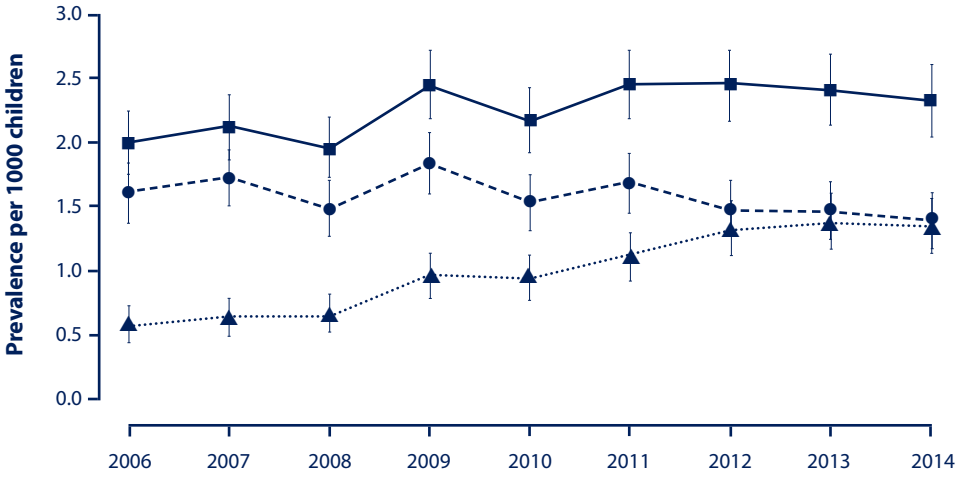

Figure 1. Prevalence (including confidence intervals) of all, old and new AED use per 1000 children (aged 0 – 19 years) per year

Prevalence of all AEDs is less than old AEDs plus new AEDs, since children could have a prescription for an old and new AED at the same time.
■ = all AEDs, ● = old AEDs, ▲ = new AEDs.

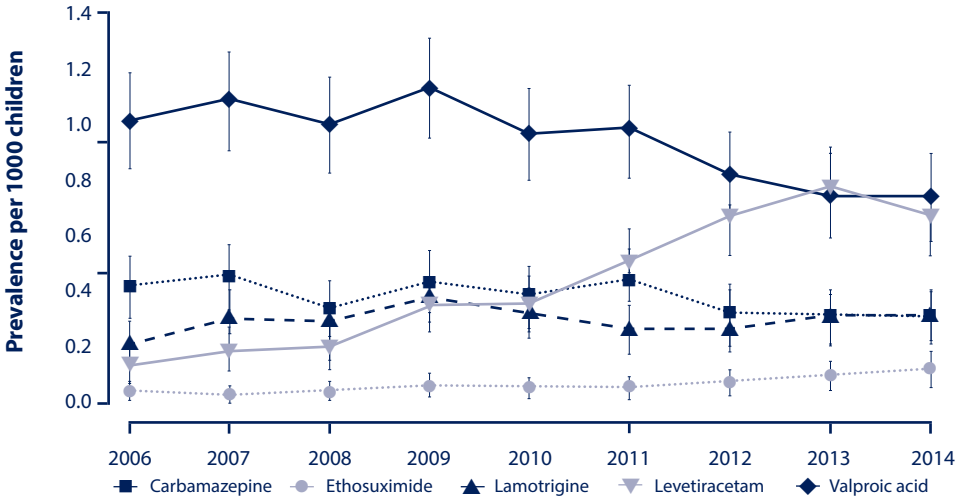

Figure 2. Prevalence of individual AED use

Prevalence (including 95% confidence intervals) of individual AED use per 1000 children (aged 0-19 years) per year of the four most often prescribed AEDs and ethosuximide.

except sulthiame (not registered in the Netherlands). Figure 2 shows the prevalence of AED use per year of the four most often prescribed AEDs and ethosuximide (prevalence of all individual AEDs are listed in supplementary Table 1). In 2006, valproic acid was by far most commonly prescribed. From 2009, the use of levetiracetam significantly increased at the expense of valproic acid and in 2012 the number of children using levetiracetam or valproic acid became more or less equal. The Dutch national epilepsy guideline from 2013, which is based on the National Institute for Health and Care Excellence (NICE) guideline, expert opinions, critical evaluation of costs, and quality of the published trials, recommends levetiracetam for all seizure types in children and adults, also as monotherapy.[15, 17] Besides levetiracetam, carbamazepine and lamotrigine are first choice for focal seizures, and valproic acid and lamotrigine (without myoclonic seizures) for generalized seizures.

The previous Dutch national guideline, published in 2006, recommended valproic acid and carbamazepine as first choice drugs for children <12 years.[20]

Of the 1484 children, 835 (56.3%) started with AED treatment between 2006 and 2014 according to our definition of an initial user. Figure 3 shows cumulative incidences of the four most often initiated AEDs and ethosuximide of these 835 users. Although clonazepam was among them, it is not shown because it is usually not prescribed for long-term use, but as emergency treatment. The most remarkable, but anticipated, finding was the decrease of initial prescribing of valproic acid and increase of initial prescribing of levetiracetam after 2010 (Figure 3). This overtake of valproic

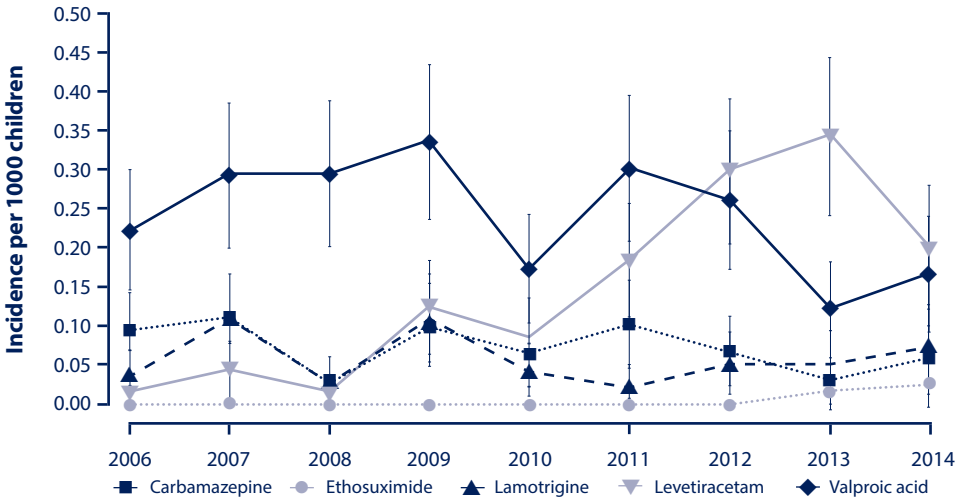

Figure 3. Cumulative incidences of individual AED use

Cumulative incidences (including 95% confidence intervals) of individual AED use per 1000 children (aged 0–19 years) per year of the four most often initiated AEDs and ethosuximide.

acid by levetiracetam was first seen in the cumulative incidences, because these represent the start of a new prescription. Since prevalence represents all prescriptions, the overtake by levetiracetam occurs only later in the prevalence figures. For the remaining AEDs the cumulative incidences remained constant and were below 0.15 per 1000 children. The incidence of ethosuximide was zero during many years, but from 2013 onwards it has been prescribed more frequently (Figure 3). In 2010, ethosuximide was shown to be relatively most effective and best tolerated in children with childhood absence epilepsy, compared to valproic acid and lamotrigine.[16] This has led to adjustments of various guidelines, both national and international.

Evaluation of the course of the therapy

In 474 (56.8%) of the 835 initial users, the course of AED prescribing with respect to monotherapy and combination therapy could be evaluated (Figure 4). The other 361 children were censored because the child was less than 90 days in the IADB.nl after the end of the treatment or the child left the database with a running prescription before 31st of December 2014. Only 26 children (5.5%) used combination therapy with an overlap of at least 90 days of two or more different AEDs; the other 448 children only had monotherapy.

The most frequent initially prescribed AED for monotherapy was valproic acid (34.2%) followed by levetiracetam (14.1%) and carbamazepine (11.6%).

Forty-two of the 395 children who used only one single AED restarted treatment with an AED after having been without AEDs for at least 6 months, most likely because of seizure recurrence; 31 (73.8%) of these children started with the same AED as they previously used.

Forty children switched from one AED to another, most likely because of inefficacy or adverse effects, which took place within 2–3 months in most children, titration schedules included.

In 13 children treatment regimen was unclear or they received two prescriptions for an AED at the same moment, but only for a very short period (< 1 month).

Regarding combination therapy, 22 of the 26 children on combination therapy started with monotherapy, 14 of them with valproic acid. Most children switched from monotherapy to combination therapy within one year. Valproic acid and levetiracetam or valproic acid and lamotrigine were most commonly prescribed as combination therapy, followed by combinations with carbamazepine and ethosuximide.

DISCUSSION

Our study of AED utilization in an unselected pediatric cohort from 2006 to 2014 shows a significant increase of prescribing of new AEDs at the expense of old AEDs, with the strongest effect for levetiracetam versus valproic acid. The overall prevalence and incidence remained constant over the years despite increased possibilities of non-medical treatment such as epilepsy surgery, vagal nerve stimulation and ketogenic diet.[21]

The annual prevalence of AED use in our study is comparable with the findings of Hsia et al.[12], who also used data from the Dutch population. They included databases in which the diagnosis was stated, which allowed them to study children with epilepsy only. The prevalence of AED use in our study was, however, almost half of the prevalence observed by van de Vrie et al.[4] They estimated that AEDs had been prescribed in 10% of the children for mood disorders and in 5% for migraine,

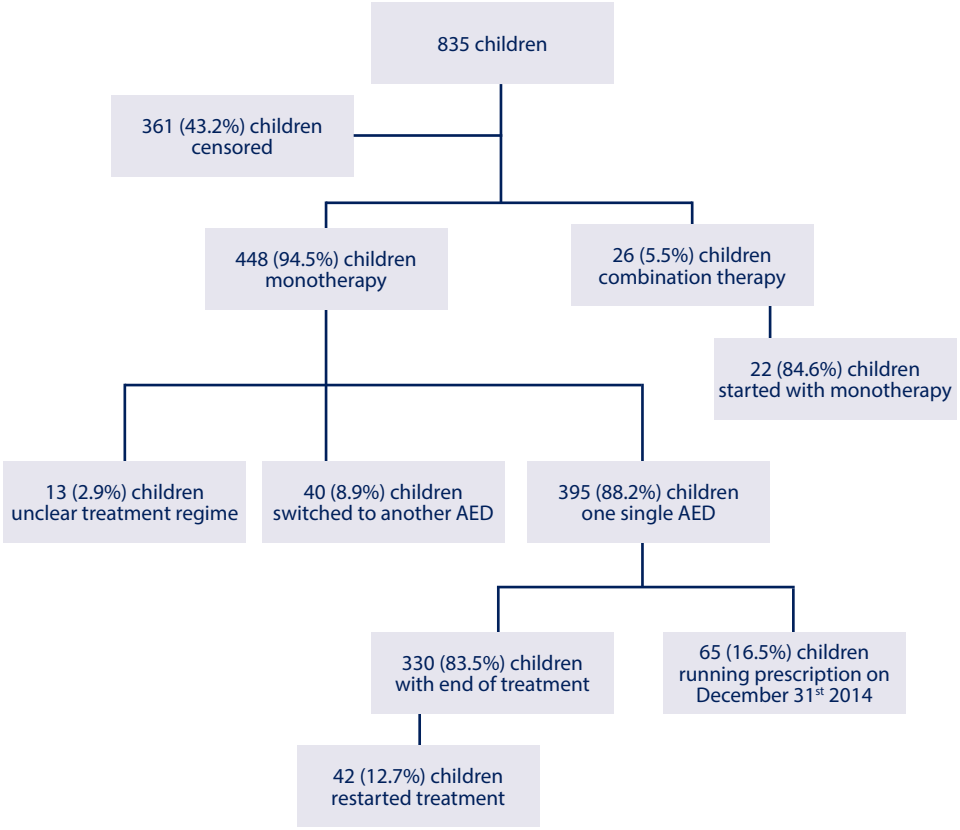

Figure 4. Flowchart of AED prescribing in our cohort

361 children were censored because the child was less than 90 days in the IADB.nl after the end of the treatment or the child left the database with a running prescription before 31st of December 2014

but these patients were included in the analyses. Using the same exclusion criteria as van de Vrie-Hoekstra, we excluded 939 (38%) children with prescriptions more likely to be for migraine or psychiatric- or mood disorders, although some of them might also have had epilepsy. Based on this evaluation, we think that children were correctly in- or excluded in our study.

The incidence of initiating an AED was highest during the first year of life (data not shown), which is in line with the peak of first seizures in children at that age.[22, 23]

Prescription of old versus new AEDs

An increase of prescribing of new AEDs at the expense of old AEDs was expected from previous studies[4-13], but was not yet observed in cohorts from before 2010. Cho et al. described an overtake of old AEDs (mainly valproic acid) by new AEDs (mainly oxcarbazepine) as first choice AED in children with different seizure types in a tertiary children's hospital between 2001 and 2012.[24] In 2014, old AEDs were still first choice in 87.5% of 694 children derived from seven specialized clinics for management of epilepsy in Jordan.[25] According to the authors this might be due to the conservative attitude of clinicians in their country when treating younger children (mean age of children in this study was 8.6 years).

Prescription of individual AEDs and current evidence

Our study showed that from 2012 onwards levetiracetam has replaced valproic acid as the most frequently prescribed first line AED in children, at least in the Netherlands. Since the introduction of levetiracetam, a linear increase of the use of levetiracetam was seen in the UK, Australia and Hong Kong, but levetiracetam did not exceed lamotrigine until 2010.[5, 7, 8, 10] The evidence for levetiracetam monotherapy in children is still very limited with only level D evidence (potentially efficacious or effective) in children with benign epilepsy with centrotemporal spikes[14], but levetiracetam is recommended for all seizure types in the Netherlands, also as monotherapy.[15] Remarkably, levetiracetam was already the most frequently prescribed AED before it was recommended in the Dutch national guideline of 2013. Apart from the effectiveness and safety profile of levetiracetam, the availability of a generic formulation since 2011 could have played a role in the increase.[26] In the NICE guideline, that takes economic aspects into account, levetiracetam is only recommended as first-line monotherapy treatment for focal or myoclonic seizures if other first-line drugs are unsuitable or not tolerated.[17] Costs are less important or not taken in account in the other guidelines.

The significant decrease in prevalence and incidence of valproic acid use was independent from sex (data not shown), whereas a stronger decrease in girls could be expected because of its teratogenicity.[29, 30]

We were not able to confirm the position of lamotrigine as the most often prescribed new drug as reported by others.[4-7, 9, 10, 12, 13] Data from the Standard And New Antiepileptic Drugs (SANAD) study from 2007, which included adults and children aged >4 years, showed that lamotrigine is clinically better than carbamazepine in focal epilepsy.[27, 28] Preference for lamotrigine over carbamazepine was also observed in three population-based studies that included children until

2009 or 2010.[7, 8, 10] Although lamotrigine is recommended for all seizure types in children and adults in the Dutch guideline, our study shows that its prescription was significantly lower than of levetiracetam from 2012 onwards, and did not change significantly over time. Its slow titration schedule, to prevent a skin rash, could be an explanation for this.

In general, evidence of efficacy (seizure freedom) and effectiveness (patient retention) of AEDs as initial monotherapy for epileptic seizures and syndromes is very limited in children; strong evidence from RCTs only exists since 1997 for oxcarbazepine in children with focal seizures and since 2010 for ethosuximide and valproic acid in children with absence seizures.[14, 16, 31] Still, only a few studies reported an increase of prescribing of oxcarbazepine, whereas other new AEDs (without sound evidence of efficacy and safety) were more often prescribed.[6, 11, 13] Only in the study of Cho et al. oxcarbazepine was the most commonly prescribed AED.[24]

We found a small but linear increase in the prescription of ethosuximide in our cohort after 2010 (Figures 2 and 3), most likely due to the publication of the study of Glauser et al. in children with childhood absence epilepsy.[16] This was not observed in the only other study that included children after 2010.[24]

Performing RCTs in children is quite complex, especially when an RCT is investigator-initiated.[32] Guidelines for treatment of children with epilepsy are therefore often based on expert opinions together with some evidence from a few well performed RCTs.[3, 14, 16, 27, 28] In clinical practice this results in prescribing new AEDs off-label.[33] The influence of costs on AED prescribing in children is uncertain, since new AEDs are prescribed in children a few years after their registration for adults and therefore closer to or even after the patent expiring date, consequently lowering its price. Last, but not least, the role of personal preferences of the local (epilepsy) specialist for certain AEDs should not be underestimated.[34]

Limitations

We describe utilization patterns of AEDs in children based on pharmacy-dispensing data from the IADB.nl; a database proven representative for the Netherlands. However, the database does not contain information about diagnosis or indication for prescription. We tried to exclude children more likely to receive AEDs for migraine and/or a psychiatric disorder as accurately as possible. However, probably this has led to the exclusion of some patients with both epilepsy and migraine or a psychiatric disorder.

Another limitation of our study is that the evaluation of the prescribing patterns of AEDs in children is based on dispensing instead of actual drug use and could only be done in 474 (56.8%) children due to our strict inclusion criteria. However, we calculated the use of AEDs in person-days, which is much more accurate than calculating person-months as done in other studies.[4, 6] Moreover, it gives the opportunity to define combination therapy as a prescription for two or more AEDs at the same time with an overlap of at least 90 days. This definition represents combination therapy better; otherwise, it could also indicate a switch from one AED to another AED with a short overlap.

CONCLUSION

Our study shows a stable overall utilization of AEDs in the last decade together with a significant increase of prescribing of new AEDs at the expense of old AEDs. The most pronounced change was seen for levetiracetam replacing valproic acid as the most frequently prescribed first line antiepileptic drug in children since 2012, even though current evidence of its efficacy and safety is limited and it is still prescribed off-label as monotherapy. An expected increase of prescribing of lamotrigine was not found. Apparently, personal preferences of the local (epilepsy) specialist for certain AEDs probably play an important role in prescribing AEDs in children.

REFERENCES

1. Kotsopoulos IA, van Merode T, Kessels FG, et al. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 2002;43:1402-1409.
2. Chung AM and Eiland LS. Use of second-generation antiepileptic drugs in the pediatric population. Paediatr Drugs 2008;10:217-254.
3. Weijenberg A, Offringa M, Brouwer OF, et al. RCTs with new antiepileptic drugs in children: a systematic review of monotherapy studies and their methodology. Epilepsy Res 2010;91:1-9.
4. van de Vrie-Hoekstra NW, de Vries TW, van den Berg PB, et al. Antiepileptic drug utilization in children from 1997-2005 - a study from the Netherlands. Eur J Clin Pharmacol 2008;64:1013-1020.
5. Ackers R, Murray ML, Besag FM, et al. Prioritizing children's medicines for research: a pharmaco-epidemiological study of antiepileptic drugs. Br J Clin Pharmacol 2007;63:689-697.
6. Landmark CJ, Fossmark H, Larsson PG, et al. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. Epilepsy Res 2011;95:51-59.
7. Cohen SA, Lawson JA, Graudins LV, et al. Changes in anticonvulsant prescribing for Australian children: implications for quality use of medicines. J Paediatr Child Health 2012;48:490-495.
8. Kwong KL, Tsui KW, Wu SP, et al. Utilization of antiepileptic drugs in Hong Kong children. Pediatr Neurol 2012;46:281-286.
9. Nicholas JM, Ridsdale L, Richardson MP, et al. Trends in antiepileptic drug utilisation in UK primary care 1993-2008: cohort study using the general practice research database. Seizure 2012;21:466-470.
10. Pickrell WO, Lacey AS, Thomas RH, et al. Trends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010. Seizure 2014;23:77-80.
11. Bourgeois FT, Olson KL, Poduri A, et al. Comparison of drug utilization patterns in observational data: antiepileptic drugs in pediatric patients. Paediatr Drugs 2015;17:401-410.
12. Hsia Y, Neubert A, Sturkenboom MC, et al. Comparison of antiepileptic drug prescribing in children in three European countries. Epilepsia 2010;51:789-796.
13. Dorks M, Langner I, Timmer A, et al. Treatment of paediatric epilepsy in Germany: antiepileptic drug utilisation in children and adolescents with a focus on new antiepileptic drugs. Epilepsy Res 2013;103:45-53.
14. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551-563.
15. Majoie HJM, Aldenkamp AP, Augustijn PB, et al. Richtlijn epilepsie. http://epilepsie.neurologie.nl/cmssite/index.php
16. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362:790-799.
17. Freeman A, Flower D, Rogers G, et al. National Clinical Guideline Centre, 2012. The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care. http://www.nice.org.uk/guidance/cg137
18. Visser ST, Schuiling-Veninga CC, Bos JH, et al. The population-based prescription database IADB.nl: Its development, usefulness in outcomes research and challenges. Expert Rev Pharmacoecon Outcomes Res 2013;13:285-292.
19. Monster TB, Janssen WM, de Jong PE, et al. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002;11:379-384.
20. van Donselaar CA, Carpay JA, Aldenkamp AP, et al. Epilepsie. Richtlijn voor diagnostiek en behandeling. https://epilepsie.neurologie.nl/t_files/Richtlijnen.def_pdf_op_site_NvvN.pdf
21. Aaberg KM, Bakken IJ, Lossius MI, et al. Short-term seizure outcomes in childhood epilepsy. Pediatrics 2018;141:10.1542/peds.2017-4016. Epub 2018 May 22.
22. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester,

Minnesota: 1935-1984. Epilepsia 1993;34:453-468.
23. Aaberg KM, Gunnes N, Bakken IJ, et al. Incidence and prevalence of childhood epilepsy: a nationwide cohort study. Pediatrics 2017;139:doi:10.1542/peds.2016-3908.
24. Cho YS, Ah YM, Jung AH, et al. Trends in antiepileptic drug prescriptions for childhood epilepsy at a tertiary children's hospital in Korea, 2001-2012. Paediatr Drugs 2015;17:487-496.
25. Albsoul-Younes A, Gharaibeh L, Murtaja AA, et al. Patterns of antiepileptic drugs use in epileptic pediatric patients in Jordan. Neurosciences (Riyadh) 2016;21:264-267.
26. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam monotherapy in children with epilepsy: a systematic review. CNS Drugs 2015;29:371-382.
27. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1000-1015.
28. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1016-1026.
29. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology 2015;85:866-872.
30. Tomson T, Battino D, Perucca E. Valproic acid after five decades of use in epilepsy: time to reconsider the indications of a time-honoured drug. Lancet Neurol 2016;15:210-218.
31. Guerreiro MM, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res 1997;27:205-213.
32. Weijenberg A, Callenbach P, Brouwer O, et al. Investigator-initiated randomized controlled trials in children with epilepsy: mission impossible? Epilepsia Open 2017;2:32-38.
33. Borges AP, Campos MS, Pereira LR. Evaluation of unlicensed and off-label antiepileptic drugs prescribed to children: Brazilian regulatory agency versus FDA. Int J Clin Pharm 2013;35:425-431.
34. Appleton RE, Freeman A, Cross JH. Diagnosis and management of the epilepsies in children: a summary of the partial update of the 2012 NICE epilepsy guideline. Arch Dis Child 2012;97:1073-1076.
35. College ter beoordeling van geneesmiddelen
Www.cbg-meb.nl

SUPPLEMENTARY DATA

Supplementary Table 1. Prevalence of AED use per 1000 children (0-19 years) per year

Prevalence	2006	2007	2008	2009	2010	2011	2012	2013	2014
Carbamazepine	0.413	0.449	0.335	0.432	0.383	0.436	0.322	0.301	0.309
Clobazam	0.022	0.051	0.03	0.059	0.051	0.044	0.082	0.061	0.1
Clonazepam	0.118	0.133	0.119	0.212	0.202	0.288	0.3	0.414	0.284
Ethosuximide	0.037	0.029	0.037	0.059	0.051	0.052	0.067	0.092	0.117
Felbamate	0	0	0	0	0.007	0.007	0	0.008	0
Gabapentin	0.074	0.051	0.074	0.103	0.145	0.236	0.247	0.23	0.234
Lacosamide	0	0	0	0	0.022	0.029	0.007	0.008	0.025
Lamotrigine	0.214	0.302	0.29	0.366	0.325	0.258	0.27	0.307	0.326
Levetiracetam	0.133	0.184	0.201	0.352	0.354	0.502	0.667	0.766	0.677
Oxcarbazepine	0.059	0.051	0.067	0.029	0.036	0.044	0.037	0.008	0.025
Phenobarbital	0.14	0.125	0.089	0.139	0.108	0.133	0.112	0.1	0.05
Phenytoin	0.044	0.044	0.015	0.044	0.051	0.044	0.022	0.038	0.025
Pregabalin	0.022	0.022	0.03	0.051	0.043	0.089	0.142	0.084	0.092
Primidone	0.007	0.007	0	0	0	0	0	0	0
Retigabine	0	0	0	0	0	0	0	0	0
Rufinamide	0	0	0	0	0	0	0.007	0.008	0.008
Stiripentol	0	0	0	0	0	0	0.007	0.008	0
Sulthiame	0	0	0	0	0	0	0	0	0
Topiramate	0.059	0.081	0.097	0.095	0.108	0.059	0.052	0.046	0.067
Valproic Acid	1.012	1.083	0.997	1.129	0.96	0.975	0.817	0.743	0.735
Vigabatrin	0.029	0.007	0.015	0.044	0.014	0.007	0.007	0.008	0.017
Zonisamide	0	0	0	0	0	0	0	0	0.008

Supplementary Table 2. Cumulative incidences of initiated AED per 1000 children (0-19 years) per year

Prevalence	2006	2007	2008	2009	2010	2011	2012	2013	2014
Carbamazepine	0.096	0.11	0.03	0.103	0.065	0.103	0.067	0.031	0.058
Clobazam	0	0.029	0.007	0.029	0.022	0.015	0.06	0.008	0.017
Clonazepam	0.037	0.044	0.059	0.095	0.036	0.096	0.082	0.207	0.067
Ethosuximide	0	0	0	0	0	0	0	0.015	0.025
Felbamate	0	0	0	0	0	0	0	0	0
Gabapentin	0.029	0.007	0.03	0.051	0.051	0.089	0.067	0.13	0.067
Lacosamide	0	0	0	0	0	0	0	0	0.008
Lamotrigine	0.037	0.11	0.03	0.11	0.043	0.022	0.052	0.054	0.075
Levetiracetam	0.015	0.044	0.015	0.124	0.087	0.185	0.3	0.345	0.2
Oxcarbazepine	0.007	0	0.015	0	0	0	0.007	0	0
Phenobarbital	0.096	0.081	0.052	0.095	0.072	0.096	0.09	0.061	0.042
Phenytoin	0	0.007	0	0.037	0.007	0.015	0.015	0	0.017
Pregabalin	0.015	0.007	0.015	0.037	0.022	0.066	0.067	0.069	0.067
Primidone	0	0	0	0	0	0	0	0	0
Retigabine	0	0	0	0	0	0	0	0	0
Rufinamide	0	0	0	0	0	0	0	0	0
Stiripentol	0	0	0	0	0	0	0	0	0
Sulthiame	0	0	0	0	0	0	0	0	0
Topiramate	0.007	0.015	0.022	0.037	0.022	0.015	0.022	0	0.025
Valproic Acid	0.221	0.295	0.3	0.337	0.174	0.303	0.262	0.123	0.167
Vigabatrin	0.007	0	0.007	0.015	0.007	0	0	0.008	0.008
Zonisamide	0	0	0	0	0	0	0	0	0

CHAPTER 4

Levetiracetam monotherapy in children with epilepsy: a systematic review

A. Weijenberg, O.F. Brouwer, P.M.C. Callenbach

CNS Drugs 2015;29:371-382

ABSTRACT

Background

Levetiracetam, a second-generation anti-epileptic drug (AED) with a good efficacy and safety profile, is licensed as monotherapy for adults and children older than 16 years with focal seizures with or without secondary generalization. However, it is increasingly being used off-label in younger children.

Objectives

We critically reviewed the available evidence and discuss the present status of levetiracetam monotherapy in children 0-16 years old.

Data sources

We systematically searched the literature using PubMed, Web of Science and Embase up to August 2014 for articles on levetiracetam monotherapy in children. Keywords were levetiracetam, monotherapy and child*. The titles and abstracts of 532 articles were evaluated by AW, of which 480 were excluded. The full-text of the other 52 articles were assessed for relevance.

Results

We covered one review, one opinion statement and 32 studies in this review, including four randomized controlled trials, ten open-label prospective studies, eight retrospective studies, and ten case reports. The formal evidence for levetiracetam monotherapy in children is minimal: it is potentially efficacious or effective as initial monotherapy in children with benign epilepsy with centrotemporal spikes. In all of the published studies, however, efficacy and tolerability of levetiracetam seemed to be good and comparable to other AEDs.

Conclusion

The data of 32 studies on levetiracetam monotherapy in children were insufficient to confirm that levetiracetam is effective as initial monotherapy for different types of seizures and/or epilepsy syndromes. There is still an urgent need for well designed trials to justify the widespread use of levetiracetam monotherapy in children of all ages.

INTRODUCTION

Levetiracetam is a second-generation anti-epileptic drug (AED) that has been on the market since 1999 in Europe as add-on therapy for adolescents from the age of 16 years with focal epilepsy.

Levetiracetam, (S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, is the (S)-enantiomer of the ethyl analogue of piracetam and shares its chemical structure with numerous nootropic drugs.[1, 2] The mechanism of action differs structurally and functionally from other currently available AEDs as it binds to the synaptic vesicle protein 2A (SV2A). The presence of SV2A in the presynaptic terminals suggests that its anti-epileptic function might be based on it affecting presynaptic events that regulate synaptic vesicle release.[3] Although its precise mechanism of action is not known, Nowak et al. [4] suggested that levetiracetam might modulate SV2 protein interactions. As a consequence, normal levels of SV2 and synaptotagmin (a SV2-binding protein) at the synapse are maintained, which may reduce seizures. It also plays a role in Ca^{2+} homeostasis by inhibiting ryanodine and IP3 receptor-dependent Ca^{2+} release from endoplasmic reticulum and by inhibiting Ca^{2+} entry through blocking of the L-type Ca^{2+} channels in hippocampal neurons.[5]

Levetiracetam is almost completely absorbed after oral administration and its bioavailability is close to 100%; it is unaffected by food.[6] Peak plasma concentrations occur in 1 h and steady state concentrations are achieved in 2 days if levetiracetam is taken twice daily. Pharmacokinetics is linear, dose proportional and time independent.[6] The distribution is close to the volume of intracellular and extracellular water and levetiracetam remains almost unattached to proteins.[7] Levetiracetam is minimally metabolized and, after 24 h, 27 % is excreted as inactive metabolites.[8] The metabolism of levetiracetam does not involve the hepatic cytochrome P450 (CYP) system, nor does it inhibit or induce hepatic enzymes.[6] The major elimination route for levetiracetam is renal; 66 % as an unchanged drug.[9] Dose adjustments are only recommended in patients with moderate to severe renal impairment or severe hepatic impairment with concomitant renal insufficiency. The body clearance of levetiracetam in children is 30-40% higher compared with adults and it is therefore recommended that children have a daily maintenance dose on a weight normalized level (20-60 mg/kg/day) divided over two doses; this is equivalent to 130-140 % of the usual daily adult maintenance dosage (1000-3000 mg/day).[10] Levetiracetam has no clinically meaningful drug-drug interactions with other AEDs, or non-AEDs such as oral contraceptives, warfarin and digoxin. Thus, because of its unique chemical structure, specific mode of action and pharmacokinetic profile, levetiracetam has become one of the most widely used second-generation AEDs for both adults and children.

Levetiracetam was licensed as add-on therapy in children in 2005. Nowadays, levetiracetam is registered in Europe and the US as add-on therapy for focal onset seizures with or without secondary generalization in patients from 1 month of age, as add-on therapy for myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy, and as add-on therapy for primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy (in Europe from 12 years of age; in the US from 6 years of age).

It was not until 2006 that it was licensed as monotherapy, but only in Europe, for adults and children from 16 years of age with focal onset seizures with or without secondary generalization. Off-label use of levetiracetam as monotherapy in younger children has increased considerably over the last decade due to its efficacy in both focal and generalized seizures, its good safety profile, favourable pharmacokinetic properties and its availability in an intravenous form for the acute setting.[11-18]

Here, we review the available evidence for the use of levetiracetam monotherapy in children in the literature, including data from randomized controlled trials. We also discuss the present status of levetiracetam and make some recommendations for future research.

METHODS

For this review, a literature search was performed by AW using PubMed (Medline), Web of Science and Embase (until August 2014) for papers on levetiracetam monotherapy in children (<18 years of age). There are no Cochrane Reviews on levetiracetam monotherapy. The following search terms were used: levetiracetam AND monotherapy AND child*. Only papers written in English, Dutch, French, or German were included. Articles were screened by AW and, in case of any dispute, discussed with PMCC. If a study included both children and adults, it was reviewed only if the results of efficacy were reported separately for children. We also searched the reference lists of these publications for more articles relevant to the topic. Abstracts of congress proceedings were not included. Data extraction from the articles was done independently by AW in Word and monitored by PMCC. We critically evaluated the study designs and whether there was any risk of bias in the individual studies.

Overview of Published Articles

The systematic literature search yielded 690 articles. After removing duplicates, the titles and abstracts of 532 articles were evaluated by AW; 480 were excluded (Figure 1). The full text of the other 52 articles were assessed for relevance and 34 articles were included in this systematic review: four randomized controlled trials (RCTs), ten open-label prospective studies, eight retrospective studies, ten case reports, a review, and an opinion statement.[12, 19-51]

Review, Opinion Statement and Case Reports

One review and one opinion statement argued that levetiracetam monotherapy should be the drug of choice in patients with juvenile myoclonic epilepsy, based on evidence from trials, especially if valproic acid is contra-indicated; for example, in women of child-bearing age.[50, 51]

Ten case reports have been published on the use of levetiracetam monotherapy in children, including neonates, with a wide variety of seizure types, epilepsy syndromes, dosages and ages (Table 1).[40-49] Dosages of levetiracetam were given in mg/kg/day or mg/day or not documented. All children became seizure-free, but the duration of follow-up was not given in three case reports (Table 1). The case reports suggested a high efficacy of treatment with levetiracetam monotherapy, and adverse events were infrequent or they were not reported.

Retrospective studies

Eight retrospective studies on levetiracetam monotherapy in children have been published, the first in 2004 (Table 2).[32-39] Most of them included patients with focal and/or generalized epilepsy. Levetiracetam dosage in these studies ranged from 10 to 108 mg/kg/day, but was mostly in the 20-40 mg/kg/day range. The mean duration of follow-up ranged from 3 to 27 months; four studies had a follow-up of more than one year.[34, 35, 37, 38] Three studies compared efficacy and tolerability of levetiracetam with carbamazepine[35], with oxcarbazepine or valproic acid[36], and with valproic acid.[38]

In all but one of the eight studies levetiracetam efficacy was considered to be good, and seizure freedom was achieved in more than 60% of patients in most studies, including those on children who had been using another AED prior to levetiracetam monotherapy (Table 2). Tolerability was good in all studies, with behavioural and cognitive changes being the most common adverse events; the discontinuation rate due to adverse events was low (0-12 %). In one study the retention rate was not significantly different between the two groups (levetiracetam vs oxcarbazepine and levetiracetam vs valproic acid), although levetiracetam monotherapy failed more often due to lack of efficacy in both groups.[36]

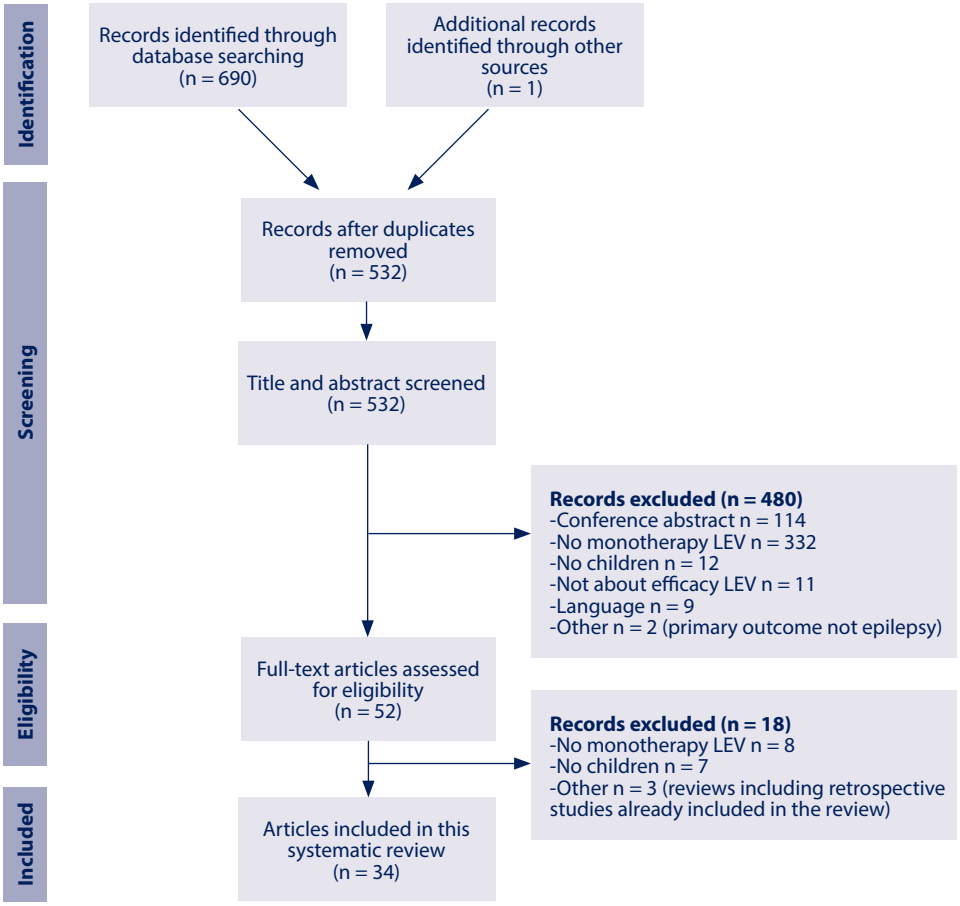

Figure 1. PRISMA flow diagram. *LEV* levetiracetam

Prospective Open-Label Studies

Lagae et al.[12] were the first to report a prospective trial on levetiracetam monotherapy in children. Since then, nine more open-label prospective studies have been published that included children, and sometimes even neonates, with different but overall relatively benign seizure types and/or epilepsy syndromes (Table 3).[23-31] In three studies levetiracetam was given in mg/day, without considering body weight, with dosages ranging from 1000 to 3000 mg/day.[23, 24, 27] In seven studies dosages were based on bodyweight, starting with 10 mg/kg/day, with increasing dosage until seizure freedom was reached, with a maximum of 70 mg/kg/day (Table 3).[12, 25, 26, 28-31] In a pilot study by Kossoff et al.[26], children were switched from carbamazepine or oxcarbazepine monotherapy to levetiracetam monotherapy.

The baseline AED was tapered off over two weeks. Verrotti et al.[24] reported on 21 children who received levetiracetam monotherapy: 12 of them were converted from monotherapy with valproic acid, carbamazepine, oxcarbazepine, or lamotrigine to levetiracetam monotherapy. However, follow-up was more than one year in only half of these trials; this is regarded as the minimum duration to draw any conclusions about long-term efficacy, adverse events and tolerability of AED treatment.[52, 53]

In most studies, efficacy of levetiracetam monotherapy was reported to be good, with a high percentage of children becoming seizure free (20-100%) or having more than 50% seizure reduction (62-100%). In one study the response was significantly better in the children who were AED-naive before initiating treatment with levetiracetam.[24] Some studies used extra outcome parameters other than efficacy, such as quality of life[12], and electroencephalography (EEG) findings and language function.[26] Lagae et al.[12] studied 10 children and observed increased alertness in three and a positive effect on behavior in one. Furthermore, median overall quality of life was higher in children on levetiracetam monotherapy than in children with add-on levetiracetam.[12] Kossoff et al.[26] evaluated EEG findings and language function in six children with benign epilepsy with centrotemporal spikes (BECTS), and they also looked for additional evidence of impaired auditory comprehension and verbal memory. After 6 months of treatment, the parents of all children reported subjective improvements, which were confirmed in most children by objective testing. The EEG had normalized in only three children.

Six trials reported the occurrence of adverse events, most commonly irritability and somnolence.[12, 24, 26, 28, 29, 31] In three, all adverse events were transient[24, 28, 29] and in two, none of the children discontinued levetiracetam because of adverse events.[12, 26] In a large study of 37 children on levetiracetam monotherapy and 83 children on levetiracetam add-on treatment, a relatively high percentage reported adverse events (47.5 %) and four of them even had to discontinue levetiracetam.[31] Results for the group treated with monotherapy were, however, not given separately.

Randomized Controlled Trials

Four RCTs have been published: two open-label parallel group trials and two double-blind trials (Table 4).[19-22] Most trials only included children with a well described epilepsy syndrome such

as BECTS [19, 22] or absence epilepsy (childhood absence epilepsy [CAE], juvenile absence epilepsy [JAE]).[20] The age at enrolment varied between 3 and 17 years. The maximum dosage of levetiracetam was 2000 mg/day in 12- to 17-year-old children [21] or 30 mg/kg/day.[19, 20, 22] One trial was placebo-controlled[20] and, for obvious ethical reasons[54], the duration of the double-blind period was only two weeks, which is much shorter than the duration of the other trials (24-78 weeks).

The equivalence open-label trial of Coppola et al.[19] compared levetiracetam with oxcarbazepine in children with BECTS and they observed no significant difference in the percentage being seizure free at 18 months (Table 4). In another trial, in children with absence epilepsy, Fattore et al.[20] showed no significant difference in seizure freedom between levetiracetam and placebo. After the two week double-blind period, the trial continued as an open-label trial and almost all children receiving the placebo were switched to levetiracetam. During long-term follow-up, 32 % (12/38) of the children initially on levetiracetam continued with levetiracetam and were seizure-free for at least 267 days; 63 % (24/38) discontinued levetiracetam because of inefficacy at a later stage. After one year, 17 children (29 %) were still seizure-free on levetiracetam (initially on levetiracetam or placebo-therapy). Rosenow et al.[21] included patients aged ≥ 12 years with newly diagnosed focal or generalized epilepsy. If patients were already using an AED, this was tapered off during the first three weeks of the study period. A post-hoc subgroup analysis was performed for 33 patients aged 12-17 years. Seizure freedom after six weeks of treatment was compared between levetiracetam and lamotrigine, although patients on lamotrigine were still in their titration period and the dosage of lamotrigine also increased after this time-point. Efficacy and tolerability of levetiracetam and lamotrigine did not differ significantly for the group aged 12-17 years. Quality of life scores (QOLIE-10) at the beginning and end of treatment (26 weeks) were similar in both treatment groups; a subgroup analysis for children aged 12-17 was not presented. In the non-inferiority trial of Borggraefe et al.[22], levetiracetam was compared with sulthiame in children with BECTS. Their primary endpoint was treatment failure, defined by seizure recurrence during the observation period. This was not significantly different between treatments (Table 4). However, the retention rate was significantly higher in the sulthiame group than in the levetiracetam group ($p = 0.03$).

The most commonly reported adverse events were somnolence and irritability or behavioral problems. Significant differences with respect to adverse events were not observed between the treatments reported. However, none of the trials used a standardized questionnaire to investigate the occurrence of adverse events.

Table 1. Case reports on levetiracetam monotherapy in children (10 studies)

References	Diagnosis	Number of children	Age (years)[a]	Maximum dosage	Follow-up of monotherapy (months)	Efficacy	AEDs prescribed before levetiracetam
Bello-Espinosa 2003[40]	BECTS	3	4 6 10	250 mg/day 1000 mg/day 500-1000 mg/day	ND	SF SF SF	None
Kossoff 2003[41]	Landau-Kleffner syndrome	1	5	500-750 mg/day (60 mg/kg)	9	SF	CBZ, VPA
Shoemaker 2007[42]	Neonatal seizures	3	0 0 0	30 mg/kg/day 30 mg/kg/day 30 mg/kg/day	ND	SF SF SF	PHB, MDZ, fos-PHT PHB, MDZ, fos-PHT fos-PHT, OXC
Papacostas 2007[43]	Tuberous sclerosis	1	7	1000 mg/day	18	SF	VPA, OXC, CBZ, TPM
Alehan 2008[44]	PRES→ non-convulsive status epilepticus	1	10	20 mg/kg/day	9	SF	PHT
García 2009[45]	Panayiotopoulos syndrome	2	8 12	2000 mg/day 1000 mg/day	36 36	SF SF	VPA VPA
Ledet 2010[46]	Neonatal seizures	1	0	40 mg/kg/day	8	SF	PHB
Harbord 2011[47]	Hemiplegic cerebral palsy and epilepsy	3	8 14 17	ND ND ND	24 36 36	SF SF SF	LTG, TPM, VPA CBZ, LTG, VPA CBZ, LTG, PHB, VPA
Arslan 2012[48]	Acquired epileptiform opercular syndrome	1	5	50 mg/kg/day	nd	SF	None
Verrotti 2013[49]	Epilepsy in patient with Cornelia de Lange syndrome	1	ND	ND	60	SF	None

[a] Age at start treatment

AEDs, anti-epileptic drugs; BECTS, benign epilepsy with centrotemporal spikes; CBZ, carbamazepine; fos-PHT, fosphenytoin; LEV, levetiracetam; LTG, lamotrigine; MDZ, midazolam; ND, no data; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; PRES, posterior reversible encephalopathy syndrome; SF, seizure free; TPM, topiramate; VPA, valproic acid.

Table 2. Retrospective studies on levetiracetam monotherapy in children (8 studies)

References	Diagnosis	Number of children	Age (years)[a]	Dosage (mg/kg/day)	Follow-up of monotherapy (months)	Efficacy (%)	% AE (% stopped due to AE)	% patients with AEDs before LEV
Koukkari 2004[32]	Focal or generalized epilepsy	19	0.8-16	20-79	ND	SF or >50% SR 58	33 (10)	0
Khurana 2007[33]	Focal or generalized epilepsy	18	2.5-18	14-60	Mean 10.4	SF 61 >50% SR 67	22 (11)	89
Sharpe 2008[34]	JME	30	8-23	10-59	Mean 27	SF 80	7 (3)	60
Perry 2008[35]	Focal epilepsy	LEV 66 CBZ 20	2.8-7.8[b] 3.4-9.3[b]	ND ND	Mean 17.1 Mean 18.5	SF 73 (at 6 months) SF 65 (at 6 months)	45 (12) 70 (5)	19.7 5
Bertsche 2014[36]	Focal epilepsy	LEV 42 OXC 34	0.5-16.7 1.9-16.9	27-108 11-71	12	Ret. LEV 50 Ret. OXC 71[d]	LEV 10 (10) OXC 12 (12)	0
	Focal or generalized epilepsy[c]	LEV 61 VPA 49	0.5-16.7 0.5-16.3	27-108 5-47	12	Ret. LEV 52 Ret. VPA 63[d]	LEV 7 (7) VPA 14 (14)	0
Chen 2014[37]	ESES	21	1.1-11.7[e]	30-60[e]	19[e]	Reduction of SWI >50% 29 Reduction of SWI <50% 33	ND (0)[e]	ND
Xiao 2014[38]	BECTS	LEV 33 VPA 23	4-11.3 4-13.5	15-38 9-31	18 18	SF 6 months 58 SF 18 months 100 SF 6 months 61[d] SF 18 months 100[d]	27 (0) 22 (0)[d]	0
Bayram 2014[39]	Focal or generalized epilepsy	9	10-16	20-50	Mean 7	SF 100	0 (0)	100

[a] Age at start treatment
[b] Interquartile range
[c] Absences were not included
[d] Not significantly different compared to LEV
[e] Total population, including both add-on and monotherapy
AE, adverse events; AEDs, anti-epileptic drugs; BECTS, benign epilepsy with centrotemporal spikes; CBZ, carbamazepine; ESES, electrical status epilepticus during sleep; JME, juvenile myoclonic epilepsy; LEV, levetiracetam; OXC, oxcarbazepine; ND, no data; Ret., retention rate; SF, seizure free; SR, seizure reduction; SWI, spike-wave index on the electroencephalogram; VPA, valproic acid.

Table 3. Prospective open-label studies on levetiracetam monotherapy (10 studies)

References	Trial design	Diagnosis	Number of children	Age (years)[a]	Dosage[b]	Follow-up	Efficacy (%)	% AE (% stopped due to AE)	Retention rate (%)
Lagae 2005[12]	OL	All seizure types	10	4-14	17-47	20 weeks	SF 20, >50% SR 90	10 (0)	90
Di Bonaventura 2005[23]	OL	diopathic generalized epilepsy	4	8-16	2000-3000 mg/day	6-10 months	SF 100	0 (0)	ND
Verrotti 2007[24]	OL, MC	BECTS	21	5-12	1000-2500 mg/day	12 months	SF or >50% SR 100	9.5 Transient (0)	100
Gümüş 2007[25]	OL	West Syndrome	5	0	30-60	4 weeks	SF 40, >50% SR 80	ND	100
Kossoff 2007[26]	OL	BECTS + language problems	6	6-12	40 mg	6 months	SF 67, improvement in language function	17 (0)	100
Verrotti 2008[27]	OL, MC	JME	32	7-16	1000-2500 mg/day	12 months	SF 91, >50% SR 100	0 (0)	100
Verrotti 2008[28]	OL, MC	CAE, JAE	21 12	5-13	31-70	6 months 12 months	SF 52 SF 100	10 Transient (0)	ND
Verrotti 2009[29]	OL, MC	COE-G	12	6-16	20-45	18 months	SF 100	17 Transient (0)	100
Fürwentsches 2010[30]	OL	Neonatal seizures	6	0	10-50	3 months	SF 100 after 6 days SF 50 after 3 months	0 (0)	ND
Li 2011[31]	OL	All seizure types	37	0-16[c]	10-60	12 months	SF 46 >75% SR 62	47.5 (3.3)[c]	73.3[c]

[a] Age at start treatment
[b] Dosage in mg/kg/day unless stated otherwise
[c] Total population, including both add-on and monotherapy
AE, adverse events; BECTS, benign epilepsy with centrotemporal spikes; CAE, childhood absence epilepsy; COE-G, childhood occipital epilepsy–Gastaut type; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; MC, multicentre; ND, no data; OL, open label; SF, seizure free; SR, seizure reduction.

Table 4. Randomized controlled trials on levetiracetam monotherapy (4 studies)

References	Trial design	Diagnosis	Number of children	Age (years)[d]	Dosage[b]	Follow-up	Efficacy (%)	AE (%) (% stopped due to AE)	Retention Rate (%)
Coppola et al.[19]	RCT, OL, PG	BECTS	LEV 21 OXC 18	3-14	LEV 20-30 OXC 20-35	18 months	LEV SF 90[c] OXC SF 72	LEV 14 (5) OXC 11 (5.5)	LEV 85.7 OXC 66.7
Fattore et al.[20]	RCT, DB, PC, MC	CAE, JAE	LEV 38 Placebo 21	4-15	LEV 30	2 weeks	LEV SF 24[c] (18 % also on EEG) Placebo SF 5 (0% on EEG)	LEV 18 Placebo 14	LEV 97.4 Placebo 100
Rosenow et al.[21]	RCT, OL, PG, MC	Focal and generalized epilepsy	LEV 17 LTG 16	12-17	LEV 1500-2000 (mg/day) LTG 150-200 (mg/day)	6 weeks 26 weeks	No difference LEV vs LT	No differences LEV vs LTG	ND
Borggraefe et al.[22]	RCT, DB, PG, MC	BECTS	LEV 21 STM 22	6-12	LEV 20-30 STM 4-6	24 weeks	LEV TF 19[c] STM TF 9.1	LEV (23.8) vs STM (4.5)[c] Except for airways: LEV 23.8 STM 63.6 ($p = 0.014$)	LEV 57.1 STM 86.4 ($p = 0.03$)

[a] Age at start treatment
[b] Dosage in mg/kg/day unless stated otherwise
[c] Not significantly different
AE, adverse event; BECTS, benign epilepsy with centrotemporal spikes; CAE, childhood absence epilepsy; DB, double blind; JAE, juvenile absence epilepsy; LEV, levetiracetam; LTG, lamotrigine; MC, multi centre; ND, no data; OL, open label; OXC, oxcarbazepine; PC, placebo controlled; PG, parallel group; RCT, randomized controlled trial; SF, seizure freedom; STM, sulthiame; TF, treatment failure

DISCUSSION

In this review, 32 studies on levetiracetam monotherapy in children are described. In all of them, efficacy and tolerability of levetiracetam monotherapy seems to be good and comparable or even favorable to other AEDs. Nonetheless, we must recognize that it has only been licensed for monotherapy in children older than 16 years in Europe.

Current Evidence for Efficacy

The most commonly used primary endpoint for efficacy was seizure freedom and/or percentage of seizure reduction (30 of 32 studies). The case reports suggested a very high efficacy of treatment with levetiracetam monotherapy. Publication bias may, however, have led to an unrealistic positive view of its efficacy. The percentage of children becoming seizure-free in both retrospective and prospective studies was 61-100 %. Only 20-46 % of cases became seizure-free in three prospective open-label studies that included children with all seizure types or even West syndrome.[12, 25, 31] Efficacy of levetiracetam does not seem to be related to age at enrolment, dosage or seizure type and/or epilepsy syndrome (Tables 1, 2, 3, 4). Since most studies included children with overall relatively benign seizure types and/or syndromes, its efficacy might be overestimated. In summary, the efficacy of levetiracetam monotherapy in children seems good and comparable to other AEDs, but the level of evidence is limited and not available for all seizure types and/or epilepsy syndromes.

Current Knowledge on Tolerability

The range of children with reported adverse events varied between 0 and 47.5 %. The percentage of children who had to stop levetiracetam treatment due to adverse events was 0-12 % in most studies, although in the trial of Borggraefe et al. [22], 23.8% of the children discontinued levetiracetam because of adverse events. The most frequently reported adverse events were behavioral and/or cognitive changes (i.e. irritability, mood disturbances or somnolence), but these complaints were mostly transient. This is in line with the most commonly reported adverse events for levetiracetam.[55] In children with pre-existing behavioral problems, the problems could exacerbate during levetiracetam therapy.[56] In some, but not all, of the prospective studies, pre-existing behavioral and/or cognitive problems were exclusion criteria.[24, 26-29] In two RCTs, children with a mental deficit or intellectual disability were excluded.[19, 20] The other two RCTs did not mention any exclusion criteria for behavioral and/or cognitive problems.[21, 22] Because children with epilepsy may develop cognitive and/or behavioral problems due to both the epilepsy itself and the treatment with AEDs, it is very important to evaluate the exact role of treatment on these problems as well.[54, 57] According to Cross et al. [58], effective management requires treatment within the context of the overall health status and quality of life of the treated child. Two trials investigated quality of life, and this was unchanged or positively influenced by the use of levetiracetam monotherapy.[12, 21]

In summary, the tolerability of levetiracetam seems to be good, with only a few adverse events that are mostly transient, even in very young children and in dosages up to 70 mg/kg/day.

Evaluation of Study Design and Methodology

According to the International League Against Epilepsy (ILAE), the best evidence for the use of levetiracetam monotherapy in children up to March 31, 2012 reached level D for children with BECTS, based on Coppola et al.'s study.[19, 53] Level D means there is one class III double-blind or open-label study, or one or more class IV clinical studies or data from expert committee reports or opinions from experienced clinicians.[53] Since 2012, two more RCTs on levetiracetam monotherapy have been published, both with a class III rating.[21, 22] Because of the inconclusive trial results of Borggraefe et al. [22], the level of evidence for levetiracetam monotherapy in BECTS did not reach level C, while the trial results of Rosenow et al. [21] could not contribute to the level of evidence for levetiracetam monotherapy in focal and generalized epilepsy because of their study design.

Prospective studies may also contribute to the level of evidence. However, eight of the ten prospective studies did not perform a formal statistical evaluation, and only one of the other two studies found a significant decrease in seizure frequency in a subgroup analysis.[12, 23-31] Although these ten studies did not contribute to the level of evidence for levetiracetam monotherapy in children, the percentage of children becoming seizure-free after the start of levetiracetam is promising, although there may well be some publication bias.

The reasons for the small number of prospective trials performed in children are pharmaceutical companies' lack of interest in such a small market when the patent has expired, and the difficulties in recruiting patients, partially due to ethical and legal aspects.[59] Moreover, in the past, separate drug trials in children were not required. As a consequence, levetiracetam is often prescribed off-label for children based on the results of trials in adults. Children, however, have a different developmental physiology, disease pathophysiology, pharmacokinetics and/or pharmacodynamics, resulting in treatment responses that are unpredictably different from those in adults.[60, 61] There is therefore an urgent need for clinical trials in children, because <50 % of medicines used in children have been properly studied in this age group.[62] For example, anti-epileptic drugs that have been registered as add-on therapy in children and/or as monotherapy in adults should also be studied as monotherapy in children; this is already obligatory for drugs now being developed.

The ILAE has described an ideal design for clinical trials in children.[53] This includes a randomized double-blind design, with adequate sample size calculations leading to a large enough study population to show non-inferiority with a ≤ 20 % relative difference between treatment arms, based on 80% power in a non-inferiority analysis versus an acceptable comparator; with retention rate or seizure freedom as the primary endpoint after a minimum of 48 weeks of treatment, and an appropriate statistical analysis. Of the four RCTs on levetiracetam in children, only two were double-blind studies.[19, 22] Remarkably, these two studies compared levetiracetam with oxcarbazepine or sulthiame in children with BECTS, whereas the level of evidence for the efficacy of both oxcarbazepine and sulthiame is low.[19, 22, 53] Carbamazepine and valproic acid would have been a more obvious choice for comparison of efficacy.[53] Furthermore, the follow-up duration in the Borggraefe et al. [22] study was only 24 weeks.

In our opinion, one of the best ways to measure efficacy, side effects and tolerability is by using retention rate, because this endpoint combines all these parameters.[52] Retention rates in the prospective open-label studies and RCTs ranged from 57.1 % to 100 % (Tables 3, 4).

One limitation of our review is that we did not include conference papers and that the literature search and screening of articles was done by only one person. Another is that we did not perform a meta-analysis. This was not possible due to the heterogeneity of the population with varying epilepsy syndromes and seizure types, the variation in study designs and the different AEDs used for comparison.

CONCLUSION AND RECOMMENDATIONS

The formal evidence for the use of levetiracetam monotherapy in children remains quite scarce: it is potentially efficacious or effective as initial monotherapy in children with BECTS. Because of the study designs and the limited number of trials, there is insufficient data available to confirm that levetiracetam is effective as initial monotherapy in children for different types of seizures and/or epilepsy syndromes, other than BECTS.

More importantly, however, in the studies we evaluated, the efficacy of levetiracetam monotherapy in children seems at least equally comparable to other AEDs. The spectrum of reported adverse events is favorable, and levetiracetam does not have a negative impact on cognition.[63] Together with its availability in an intravenous form, unique chemical structure, novel mode of action and pharmacokinetic profile, levetiracetam may become one of the most important AEDs in treating children with epilepsy.

To formally justify the widespread use of levetiracetam monotherapy in children of all ages, we need more well conducted, double-blind RCTs to evaluate the efficacy, side effects and tolerability of levetiracetam monotherapy in children.

ACKNOWLEDGEMENTS

We thank Ms J. Senior for editing the final version of the text.

REFERENCES

1. Shorvon S. Pyrrolidone derivatives. Lancet 2001;358:1885-1892.
2. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet 2004;43:707-724.
3. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci U S A 2004;101:9861-9866.
4. Nowack A, Malarkey EB, Yao J, et al. Levetiracetam reverses synaptic deficits produced by overexpression of SV2A. PLoS One 2011;6:e29560.
5. Deshpande LS and Delorenzo RJ. Mechanisms of levetiracetam in the control of status epilepticus and epilepsy. Front Neurol 2014;5:11.
6. UCB. Keppra (levetiracetam 250, 500, 750 and 1000 mg tablets and 100 mg/ml for solution of infusion): summary of product characteristics. London: European Medicine Agency; 2010.
7. Doheny HC, Ratnaraj N, Whittington MA, et al. Blood and cerebrospinal fluid pharmacokinetics of the novel anticonvulsant levetiracetam (UCB L059) in the rat. Epilepsy Res 1999;34:161-168.
8. Perucca E and Bialer M. The clinical pharmacokinetics of the newer antiepileptic drugs. focus on topiramate, zonisamide and tiagabine. Clin Pharmacokinet 1996;31:29-46.
9. Walker MC and Patsalos PN. Clinical pharmacokinetics of new antiepileptic drugs. Pharmacol Ther 1995;67:351-384.
10. Pellock JM, Glauser TA, Bebin EM, et al. Pharmacokinetic study of levetiracetam in children. Epilepsia 2001;42:1574-1579.
11. Tan MJ and Appleton RE. Efficacy and tolerability of levetiracetam in children aged 10 years and younger: A clinical experience. Seizure 2004;13:142-145.
12. Lagae L, Buyse G, Ceulemans B. Clinical experience with levetiracetam in childhood epilepsy: an add-on and mono-therapy trial. Seizure 2005;14:66-71.
13. Glauser TA, Ayala R, Elterman RD, et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology 2006;66:1654-1660.
14. Callenbach PM, Arts WF, ten Houten R, et al. Add-on levetiracetam in children and adolescents with refractory epilepsy: results of an open-label multi-centre study. Eur J Paediatr Neurol 2008;12:321-327.
15. Chung AM and Eiland LS. Use of second-generation antiepileptic drugs in the pediatric population. Paediatr Drugs 2008;10:217-254.
16. van de Vrie-Hoekstra NW, de Vries TW, van den Berg PB, et al. Antiepileptic drug utilization in children from 1997-2005 - a study from the Netherlands. Eur J Clin Pharmacol 2008;64:1013-1020.
17. Legros B, Boon P, De Jonghe P, et al. Opinion of Belgian neurologists on antiepileptic drug treatment in 2006: Belgian study on epilepsy treatment (BESET-2). Acta Neurol Scand 2009;120:402-410.
18. Hsia Y, Neubert A, Sturkenboom MC, et al. Comparison of antiepileptic drug prescribing in children in three European countries. Epilepsia 2010;51:789-796.
19. Coppola G, Franzoni E, Verrotti A, et al. Levetiracetam or oxcarbazepine as monotherapy in newly diagnosed benign epilepsy of childhood with centrotemporal spikes (BECTS): an open-label, parallel group trial. Brain Dev 2007;29:281-284.
20. Fattore C, Boniver C, Capovilla G, et al. A multicenter, randomized, placebo-controlled trial of levetiracetam in children and adolescents with newly diagnosed absence epilepsy. Epilepsia 2011;52:802-809.
21. Rosenow F, Schade-Brittinger C, Burchardi N, et al. The LaLiMo trial: lamotrigine compared with levetiracetam in the initial 26 weeks of monotherapy for focal and generalised epilepsy--an open-label, prospective, randomised controlled multicenter study. J Neurol Neurosurg Psychiatry 2012;83:1093-1098.
22. Borggraefe I, Bonfert M, Bast T, et al. Levetiracetam vs. sulthiame in benign epilepsy with centrotemporal spikes in childhood: a double-blinded, randomized, controlled trial (German HEAD study). Eur J Paediatr Neurol 2013;17:507-514.

23. Di Bonaventura C, Fattouch J, Mari F, et al. Clinical experience with levetiracetam in idiopathic generalized epilepsy according to different syndrome subtypes. Epileptic Disord 2005;7:231-235.
24. Verrotti A, Coppola G, Manco R, et al. Levetiracetam monotherapy for children and adolescents with benign rolandic seizures. Seizure 2007;16:271-275.
25. Gumus H, Kumandas S, Per H. Levetiracetam monotherapy in newly diagnosed cryptogenic west syndrome. Pediatr Neurol 2007;37:350-353.
26. Kossoff EH, Los JG, Boatman DF. A pilot study transitioning children onto levetiracetam monotherapy to improve language dysfunction associated with benign rolandic epilepsy. Epilepsy Behav 2007;11:514-517.
27. Verrotti A, Cerminara C, Coppola G, et al. Levetiracetam in juvenile myoclonic epilepsy: Long-term efficacy in newly diagnosed adolescents. Dev Med Child Neurol 2008;50:29-32.
28. Verrotti A, Cerminara C, Domizio S, et al. Levetiracetam in absence epilepsy. Dev Med Child Neurol 2008;50:850-853.
29. Verrotti A, Parisi P, Loiacono G, et al. Levetiracetam monotherapy for childhood occipital epilepsy of Gastaut. Acta Neurol Scand 2009;120:342-346.
30. Furwentsches A, Bussmann C, Ramantani G, et al. Levetiracetam in the treatment of neonatal seizures: a pilot study. Seizure 2010;19:185-189.
31. Li J, Xiao N, Chen S. Efficacy and tolerability of levetiracetam in children with epilepsy. Brain Dev 2011;33:145-151.
32. Koukkari MW and Guarino EJ. Retrospective study of the use of levetiracetam in childhood seizure disorders. J Child Neurol 2004;19:944-947.
33. Khurana DS, Kothare SV, Valencia I, et al. Levetiracetam monotherapy in children with epilepsy. Pediatr Neurol 2007;36:227-230.
34. Sharpe DV, Patel AD, Abou-Khalil B, et al. Levetiracetam monotherapy in juvenile myoclonic epilepsy. Seizure 2008;17:64-68.
35. Perry S, Holt P, Benatar M. Levetiracetam versus carbamazepine monotherapy for partial epilepsy in children less than 16 years of age. J Child Neurol 2008;23:515-519.
36. Bertsche A, Neininger MP, Dahse AJ, et al. Initial anticonvulsant monotherapy in routine care of children and adolescents: levetiracetam fails more frequently than valproate and oxcarbazepine due to a lack of effectiveness. Eur J Pediatr 2014;173:87-92.
37. Chen XQ, Zhang WN, Yang ZX, et al. Efficacy of levetiracetam in electrical status epilepticus during sleep of children: a multicenter experience. Pediatr Neurol 2014;50:243-249.
38. Xiao F, An D, Deng H, et al. Evaluation of levetiracetam and valproic acid as low-dose monotherapies for children with typical benign childhood epilepsy with centrotemporal spikes (BECTS). Seizure 2014;23:756-761.
39. Bayram E, Topcu Y, Tufekci O, et al. The efficacy and safety of levetiracetam in paediatric patients treated with chemotherapeutic agents for haematologic disorders. J Paediatr Child Health 2014;50:553-556.
40. Bello-Espinosa LE and Roberts SL. Levetiracetam for benign epilepsy of childhood with centrotemporal spikes-three cases. Seizure 2003;12:157-159.
41. Kossoff EH, Boatman D, Freeman JM. Landau-Kleffner syndrome responsive to levetiracetam. Epilepsy Behav 2003;4:571-575.
42. Shoemaker MT and Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. J Child Neurol 2007;22:95-98.
43. Papacostas SS, Papathanasiou ES, Myrianthopoulou P, et al. Tuberous sclerosis successfully treated with levetiracetam monotherapy: 18 months of follow-up. Pharm World Sci 2007;29:350-352.
44. Alehan F, Ozcay F, Haberal M. The use of levetiracetam in a child with nonconvulsive status epilepticus. J Child Neurol 2008;23:331-333.
45. Garcia C and Rubio G. Efficacy and safety of levetiracetam in the treatment of Panayiotopoulos syndrome. Epilepsy Res 2009;85:318-320.

46. Ledet DS, Wheless JW, Rubnitz JE, et al. Levetiracetam as monotherapy for seizures in a neonate with acute lymphoblastic leukemia. Eur J Paediatr Neurol 2010;14:78-79.
47. Harbord MG. Levetiracetam in children and adolescents with epilepsy and hemiplegic cerebral palsy. J Paediatr Child Health 2011;47:302-304.
48. Arslan M, Yis U, Vurucu S, et al. Acquired epileptiform opercular syndrome: F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) findings and efficacy of levetiracetam therapy. Epilepsy Behav 2012;25:50-53.
49. Verrotti A, Agostinelli S, Prezioso G, et al. Epilepsy in patients with Cornelia de Lange syndrome: a clinical series. Seizure 2013;22:356-359.
50. Mantoan L and Walker M. Treatment options in juvenile myoclonic epilepsy. Curr Treat Options Neurol 2011;13:355-370.
51. Montouris G and Abou-Khalil B. The first line of therapy in a girl with juvenile myoclonic epilepsy: should it be valproate or a new agent? Epilepsia 2009;50 Suppl 8:16-20.
52. Weijenberg A, Offringa M, Brouwer OF, et al. RCTs with new antiepileptic drugs in children: a systematic review of monotherapy studies and their methodology. Epilepsy Res 2010;91:1-9.
53. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551-563.
54. Seidenberg M, Pulsipher DT, Hermann B. Cognitive progression in epilepsy. Neuropsychol Rev 2007;17:445-454.
55. Lyseng-Williamson KA. Levetiracetam: a review of its use in epilepsy. Drugs 2011;71:489-514.
56. Verrotti A, D'Adamo E, Parisi P, et al. Levetiracetam in childhood epilepsy. Paediatr Drugs 2010;12:177-186.
57. Plioplys S, Dunn DW, Caplan R. 10-year research update review: psychiatric problems in children with epilepsy. J Am Acad Child Adolesc Psychiatry 2007;46:1389-1402.
58. Cross JH, Kluger G, Lagae L. Advancing the management of childhood epilepsies. Eur J Paediatr Neurol 2013;17:334-347.
59. Amann JP, Glauser T, Chiron C. Developing antiepileptic drugs in children: balancing protection and access. Handb Clin Neurol 2013;111:741-746.
60. Caldwell PH, Murphy SB, Butow PN, et al. Clinical trials in children. Lancet 2004;364:803-811.
61. Klassen TP, Hartling L, Craig JC, et al. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS Med 2008;5:e172.
62. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000;320:79-82.
63. Ijff DM and Aldenkamp AP. Cognitive side-effects of antiepileptic drugs in children. Handb Clin Neurol 2013;111:707-718.

CHAPTER 5

Investigator-initiated randomized controlled trials in children with epilepsy: mission impossible?

A. Weijenberg, N. Doornebal, F.E. Jansen, E.A.J. Peeters, R. ten Houten, J. Nicolai, E.E.O. Hagebeuk, H. Stroink, M.C.Y. de Wit, P.M.C. Callenbach, O.F. Brouwer

Epilepsia Open 2017;2;32-38

SUMMARY

Objective

In children many antiepileptic drugs (AEDs) are prescribed off-label due to a lack of well-designed randomized controlled trials (RCTs). We conducted a multicenter RCT in the Netherlands to compare levetiracetam and valproic acid as monotherapy in children with newly diagnosed epilepsy. After 2 years, we had to stop this investigator-initiated trial prematurely because the inclusion rate was too low. We analyzed the reasons for this failure, assessed the various issues involved in performing RCTs in children, and now give recommendations for future studies.

Methods

A questionnaire was completed by all investigators involved in the study. It included questions about the motivation to participate and the perceived reasons for recruitment failure. We also studied literature about financial, logistic, legal, and ethical aspects of RCTs in children.

Results

Main reasons for recruitment failure were overestimation of the number of eligible AED-naive children referred by general pediatricians; personal preferences of investigators for specific antiepileptic drugs; and the extensive administrative load due to extra regulations and guidelines for children. Fundraising for investigator-initiated trials is difficult and the majority of RCTs concerning AEDs are sponsored by pharmaceutical companies. Involving children requires balancing between protection and participation; the randomization procedure and obtaining informed consent are complex for both children and parents.

Significance

Performing RCTs with AEDs in children is important but complicated by logistic, regulatory, legal and ethical restrictions. Based on our recent experience, our advice to colleagues who are planning a similar trial would be to perform a feasibility pilot study; to set up intensive collaboration with referring pediatricians; to arrange support of a clinical trials unit and a local research nurse during the complete trial period; and to incorporate the possibility of extending the recruitment period. Major investments, both financially from governmental organizations and in time, are imperative for independent RCTs in children.

INTRODUCTION

Epilepsy is one of the most common neurological disorders in childhood, with an estimated incidence of 82/100,000 children per year.[1] Seizures are most commonly treated with antiepileptic drugs (AEDs). During the last 25 years, the number of available AEDs has increased considerably.[2] Few of the newer AEDs are licensed for monotherapy use in children, such as lamotrigine, oxcarbazepine and topiramate, but the majority are still prescribed off-label. For several reasons, efficacy and tolerability of new AEDs need to be tested in children separately.[3, 4] Recently, the International League Against Epilepsy concluded that there is a lack of well-designed, properly conducted randomized controlled trials (RCTs) concerning initial monotherapy for epilepsy, especially in children.[5] It proposed an ideal design for such RCTs, with either effectiveness (patient retention) or efficacy (seizure freedom) as primary endpoint, a minimum of 48 weeks treatment for all seizure types, double-blind design, and use of an acceptable comparator.[5, 6]

We recently conducted a multicenter RCT in the Netherlands to compare levetiracetam (LEV) and valproic acid (VPA) as monotherapy in children with newly diagnosed epilepsy (LEV-VPA Study, NTR3784). We aimed to provide the highest level of evidence (level A) for LEV monotherapy in children instead of the current level D evidence.[5, 7] Unfortunately, we had to stop the trial prematurely because the recruitment rate was too low.

To learn from this experience and to help others to prevent a similar disappointment, we critically analyzed the reasons for the failure of our trial. We also assessed the various issues involved in performing these clinical trials including financial, logistic, legal, and ethical aspects. Finally, we give some recommendations to those colleagues who are planning an RCT in children.

LEV-VPA STUDY

The aim of this double-blind, multi-center trial was to investigate the efficacy, safety, and tolerability of LEV monotherapy versus VPA monotherapy as first-line treatment in children aged 4-16 years with newly diagnosed epilepsy in the Netherlands. Nine pediatric neurologists from four academic centers and five general hospitals participated, covering an estimated referral area of 70% of the total Dutch pediatric population of almost 2 million children aged 5-15 years. We calculated approximately 1,150 children with newly diagnosed epilepsy might be identified as possible candidates for our study each year. Potential recruitment was based on the experience with the Dutch Study of Epilepsy in Childhood (DSEC), in which 350 children aged 4-16 years with newly diagnosed epilepsy were included in 4 years in four hospitals.[8] On the basis of these figures, it should be possible to recruit 200 children within two years. We visited regional hospitals and informed pediatricians about the study. After explanation of the trial, we asked them to participate by referring eligible children promptly to one of the nine participating centers without starting treatment. After informed consent, children were randomized for double-blind treatment with LEV (15-60 mg/kg/day) or VPA (10-40 mg/kg/day) monotherapy if they had had at least two seizures in the last 4 weeks before enrolment without having received any previous antiepileptic treatment for their seizures except for emergency medication. Because of the variation in bodyweight, capsules with five different dosages had to be produced to allow slow increases in dosage and to prevent children having to swallow a large number of capsules per day. The appropriate dosage of medication was transported to the individual centers directly after randomization. Children were treated for a maximum of 52 weeks with trial medication. Neuropsychological questionnaires and assessments were performed at the start and during the trial. Primary endpoint was retention rate after 52 weeks of treatment.

According to our power analysis for a noninferiority survival type trial, we calculated a needed sample size of 196 children to achieve 80% power to detect a noninferiority margin difference between the group proportions of -0.1600 (based on recommendations of the International League Against Epilepsy [ILAE] for noninferiority trials), assuming the retention rate for VPA to be 0.8000 (one-sided Z test [pooled], $p = 0.0253$).[6] Funding for this investigator-initiated trial was obtained from the Netherlands Organisation for Health Research and Development (ZonMW).

During a pretrial period of 3 years, the following tasks were completed: the protocol was written and approved by all participating investigators; funding was obtained; regional hospitals were visited, informed and asked to participate; trial medication was manufactured; logistics concerning randomization, trial procedures and electronic case report (eCRF) design were effectuated; and approval from ethical committees and boards of directors was obtained. The trial started in February 2013, but, because of administrative procedures, it took until December 2013 before the last center had permission to start inclusion. At the end of 2013, we had included only 4 children instead of the planned-for 100. To improve the inclusion rate, we amended our inclusion criteria: the youngest age of inclusion was lowered from 4 to 2 years, a minimal seizure frequency before entry was no longer required, and previous treatment with AEDs other than LEV or VPA was allowed,

provided this had been withdrawn at least 1 year before inclusion. An extra year of inclusion was anticipated, but despite these adjusted inclusion criteria, the inclusion rate remained too low. In July 2014, 18 months after the start of the study, we had included 15 children with only five of the nine participating hospitals having been able to include at least one patient. We then decided to stop the trial.

Evaluation of the LEV-VPA study

Because of the disappointing premature discontinuation of the trial, we determined that the trial needed to be systematically evaluated. A questionnaire was sent out and returned by all nine investigators (see supplementary data). It included questions about the motivation to participate and the perceived reasons for recruitment failure. One investigator could not include any patient due to personal circumstances and did not fully complete the questionnaire.

The most important motivation of the investigators to participate had been the lack of sound evidence of efficacy and safety of LEV in children and the fact that they still had to prescribe LEV monotherapy off-label since this drug is only registered as add-on treatment in children. They hoped that the results of this trial justified prescription of LEV as monotherapy and that, as a consequence, it could be registered for monotherapy in children.

The investigators gave several reasons for the low number of inclusions and failure of our trial. Most important was the extensive administrative load, e.g., getting approval of the board of directors for each hospital, obtaining written informed consent from both parents, handling emails from the trial coordinator and monitor, as well as having to complete a detailed eCRF and to follow many trial procedures. The heavy paperwork even withheld three centers from including any patient. Most investigators were convinced that more administrative support, for instance, from a research nurse, would have increased inclusion rate. This could have been achieved by financial support for every participating center to guarantee enough assistance.

Table 1 shows the other reasons for the low number of inclusion. The first reason was the investigator clinicians' preference for another AED in individual cases. One investigator wished to avoid prescribing VPA in girls (of any age); another investigator did not want to include children with childhood absences following the US RCT by Glauser et al.[9] that showed ethosuximide to be superior to valproate and lamotrigine. The results of this study were published during the grant application procedure of the LEV-VPA study, and no adaptations were made in our study protocol after publication of this trial. Nevertheless, every treating physician always kept the possibility not to include a patient because of personal preference for a specific treatment. However, we underestimated the influence of these personal preferences. A second common reason was refusal of parents to participate, for example, because they wanted to know which AED their child would receive before randomization. Training in communication about shared decision making with parents and children might have helped the investigators.[10] Another reason was an explosive seizure onset in some children that did not allow waiting for written informed consent and subsequent arrival of trial medication. The difficulty of including children requiring very urgent

treatment might have been prevented by storage of study medication in each participating center but would have created higher storage costs. Moreover, because of the capsules with five different dosages and an unknown number of patients of each weight category to be included per participating center beforehand, an overload of study medication should have been produced, with a subsequent waste. Despite the amended inclusion criteria, the number of eligible children remained too low. Based on the figures of the DSEC, we had considered recruitment of 200 children to be possible within 2 years in our nine centers in close cooperation with pediatricians of regional hospitals.[8] However, our study was not an observational study like the DSEC, which was performed in the nineties of the last century, when commitment to participate in studies seemed to be higher. Furthermore, during the DSEC, most children were directly seen by pediatric neurologists, whereas nowadays they will generally first visit a local pediatrician. Our attempts to persuade regional pediatricians to refer children with newly diagnosed untreated epilepsy to one of the nine participating centers appeared to be in vain. In many cases these colleagues had already started medication before getting in touch with us. Logistically and financially (e.g., extra monitoring, participation of more pharmacies), it was not possible to carry out our multicenter trial in more than nine centers. Performing a feasibility study beforehand would probably have given a better indication of the expected recruitment rate in our trial.

Table 1. Reasons for not being able to include children, as given by eight investigators

	Frequency[a] (%)
Doctor's preference for a specific antiepileptic drug	5 (62)
Child/parents refused to participate	4 (50)
Too few children meeting inclusion criteria	4 (50)
Urgent antiepileptic treatment was required	2 (25)
Child became (spontaneously) seizure free (without treatment)	1 (12)

[a] Number of investigators giving this reason

RCTS IN CHILDREN WITH EPILEPSY

Few well-executed RCTs comparing old and/or new AEDs in children with epilepsy have been performed,[11] and only two of them contributed level A evidence.[5, 9, 12] Results of AED trials performed in adults are often extrapolated to children. Extrapolation may be justified for add-on therapy in children from 2 to 18 years with focal seizures.[13] However, specific research in children is necessary because of the various seizure types and many different epilepsy syndromes that occur only in childhood and the differences in pharmacokinetics and pharmacodynamics in children and adults.[11, 13] The importance of RCTs in children has been well recognized and has led to the Paediatric Regulation in the European Union in 2007[14] as well as initiatives such as the European Network of Paediatric Research (Enpr-EMA),[15] Priority Medicines for Children (PrioMedChild)[16] and StaR Child Health.[17] These networks aim to increase availability of registered drugs for children, with development of guidelines for clinical trials in children, as well as facilitating collaborations and supporting such studies financially. Performing an RCT in children, however, is challenging and several issues need to be addressed.[18, 19]

Financial aspects

All currently published relevant RCTs concerning AEDs that have been performed in children with epilepsy were partially or fully sponsored by pharmaceutical companies. The primary goal of these trials was AED registration, and most of these were performed in adults with additional inclusion of a few children. Pharmaceutical companies have no financial incentive to carry out trials with any drug for which the patent has expired or is about to expire or to perform trials for a relatively small market, such as children with epilepsy. Fortunately, nowadays the Paediatric Regulation requires that all applications for marketing authorization of new medicines include the results of studies performed in children, as described in an agreed pediatric investigation plan. The only exception to this rule is when the medicine is likely to be ineffective, inappropriate, or unsafe for children.[14] If registration is extended to children, the patent will be prolonged for 6 months.

In contrast to research by pharmaceutical companies, investigator-initiated research depends on availability of funding. Only 4 of the 28 monotherapy trials in children with epilepsy recorded in Trial Registers (ClinicalTrials.gov, ISRCTN.com, or clinicaltrialsregister.eu) are investigator-initiated, one of them being our LEV-VPA trial (Table 2). Two studies are funded by the National Institute for Health Research (United Kingdom), and one by the Dutch National Epilepsy Fund (NEF) in cooperation with the Wilhelmina Research Fund (WKZ fund) (the Netherlands). These three investigator-initiated trials are still recruiting. The other registered trials are all sponsored by pharmaceutical companies. One of these trials was prematurely stopped because the recruitment rate was too low, 18 trials have been completed, and 5 trials are on-going. The results of only 6 of the 18 successfully completed trials have been published,[20-25] and results of another 3 trials have been described on ClinicalTrials.gov, but are not (yet) published.

To support studies in children in both Europe and the United States, special programs are offered. Studies in children require the same adequate infrastructure as RCTs in adults. Costs for RCTs in

Table 2. Four investigator-initiated monotherapy trials in children with epilepsy found in Trial Registers

Study acronym	Funding	AED	Age category	Seizure type/ syndrome	Number of patients	Duration of the study treatment (duration of inclusion)
LEV-VPA	ZonMW	LEV vs. VPA	2-16 years	All	200	1 year (2 years)
SANAD II	NIHR	A. LEV vs. LTG vs. ZNS	≥5 years	A. Focal	A. 990	2 years (3.5 years)
		B. LEV vs. VPA		B. Generalized or unclassified	B. 520	
EcLiPSE	NIHR	LEV i.v. vs. PHT i.v.	6 months -18 years	Status epilepticus	308	14 days (3 years)
Rescue ESES	NEF + WKZ fund	Steroids vs. CLB	2-12 years	ESES + cognitive deficit	130	6 months (47 months)

AED, antiepileptic drug; CLB, clobazam; EcLiPSE, Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children; ESES, electrical status epilepticus in sleep; i.v., intravenous; LEV, levetiracetam; LEV-VPA, double-blind randomized trial comparing efficacy, safety, and tolerance between levetiracetam monotherapy and valproic acid monotherapy in children with newly diagnosed epilepsy; LTG, lamotrigine; NEF, Dutch National Epilepsy Fund; NIHR, National Institute for Health Research; PHT, phenytoin; Rescue ESES, Randomized European Trial of Steroids vs. Clobazam Usage for Encephalopathy with ESES; SANAD II, a comparison of Standard and New Antiepileptic Drugs; vs., versus; VPA, valproic acid; WKZ Fund, Wilhelmina Research Fund; ZonMW, Netherlands Organisation for Health Research and Development; ZNS, zonisamide.

children are, therefore, at least as high, if not higher, compared to those in adults.[26] These extra costs are mainly caused by the large range of bodyweights and age categories. In our LEV-VPA study we had to use different tests and questionnaires for neuropsychological assessments in children of many different age groups. Because of the capsules with five different dosages, the appropriate medication could only be transported to the individual centers after randomization, leading to more costs for production and distribution. More than 13% of our budget was spent on development and production of trial medication and a similar percentage on distribution. An alternative for these investigator-carried costs could be that pharmaceutical companies provide trial medication free of charge, as was done in the successful trial of Glauser et al.[9] Our total trial budget was €711,050 for 200 children, which means €3,555 per randomized child. The EcLiPSE study group (Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children; www.eclipse-study.org.uk), an investigator-initiated, 3-year, randomized open-label trial on LEV versus phenytoin monotherapy in status epilepticus in children, is funded by the National Institute for Health Research. It aims to include 308 patients in 25 centers, with a total budget of £1,515,580, which means approximately €7,000 per child. These amounts for investigator-initiated trials seem small compared to the budgets spent by pharmaceutical companies, for whom €100,000 per randomized child is rather rule than exception.

Logistics and recruitment

Performing a trial according to good clinical practice guidelines implicates an extensive and strict administrative load for each investigator. RCTs in children are even more complicated and time-consuming than those in adults because of extra regulations and body-weight-based medication. Help of research nurses in participating centers and support by a trial coordinator and clinical trials unit is therefore essential. Realistic calculation of the number of patients who can be included is one of the most important issues of every trial. A feasibility study is the best way to overcome recruitment problems. Recently, an industry-sponsored study had to stop prematurely because the inclusion rate was too low (44 instead of 120 patients in 18 months), and the limited trial budget did not allow extension.[27] In two successful monotherapy trials that provided level A evidence, the recruitment period was 51 (initially unknown) and 40 (initially planned 36) months, respectively.[9, 12] Although details on planned and real duration of the inclusion period are not known, in many trials start of recruitment was delayed and period of recruitment had to be extended. Because of these known recruitment issues, the inclusion period should be longer than expected beforehand.

Specifically in monotherapy studies, children with newly diagnosed epilepsy must be included before initiation of treatment. These children are most often primarily seen by a general pediatrician, instead of a pediatric neurologist. To be able to include a sufficient number of AED-naive children, we therefore tried to increase the awareness of this study and involve general pediatricians of regional hospitals before the start of the study. Unfortunately, this did not result in many referrals. This is probably the most important reason of failure of our study.

In addition, the investigators, all experienced specialized pediatric neurologists, often had different personal preferences for a certain AED instead of randomizing children for trial medication. Although

we knew some of these preferences beforehand, we underestimated their influence. Prescribing medication off-label based on personal treatment choices seems to be rather easily accepted as routine care, and the need to persuade doctors, children and their parents to participate in trials seems limited.[28]

Legal and ethical considerations

Nowadays it is accepted that children participate in RCTs, but it is difficult to keep a good balance between protection and access, and to meet all the bureaucratic conditions.[18] If children are involved in epilepsy research, the research should be of high quality with an adequate sample size. RCTs including mainly adults but also children should at least describe the results for these children separately, which is not always the case.[29] Placebo-controlled trials are undesirable because of ethical limitations, and children with drug-resistant focal epilepsy have been reported to show a greater response to placebo compared to adults.[3, 30] A children's research network in which multidisciplinary, cross-institutional groups are formed of (non)clinical child health researchers with access to diagnostic and laboratory facilities suitable for children, encouraging children and families to work closely with researchers in a so-called partnership forum, could be an ideal way for collecting data and focusing on specific issues.[31]

The randomization procedure itself is generally poorly understood by parents,[32] or they think that doctors already know which treatment is better. Even in our trial, with two established first-choice AEDs, randomization was one of the reasons for parents to refuse participation. Obtaining informed consent is also an issue because in the Netherlands both parents need to give permission, and from 12 years of age the child must sign as well.[33] As shown in the Informed Consent and Assent Tool kit, differences between national consent procedures exist in Europe.[34] Especially for international studies, a uniform guideline is desirable.

CONCLUSION

The design of the LEV-VPA study corresponded to the proposed design of the ILAE for a noninferiority RCT in children with an acceptable comparator and a sample size large enough to show noninferiority with a ≤ 20% relative difference between treatment arms.[6] Despite the sound methodological design and a motivated group of experienced investigators, our trial still had to end prematurely. The intended collaboration with regional pediatricians did not succeed, and we were not able to recruit enough children. Other important aspects that played a role were the personal preferences of the doctors and the extensive administrative load.

Although the ILAE recognizes problems in performing RCTs in children, they do not give recommendations on how to realize more successful trials in children.[5, 6] Despite differences in national guidelines and governance requirements, most encountered problems when performing RCTs in children are not country specific. The chance of success could be increased by: (1) a feasibility pilot study; (2) better prepared and more intensive collaboration with referring regional pediatricians; (3) support of a clinical trials unit during the complete trial period; (4) local support of a well-trained research nurse in every participating center to handle the administrative load during both the pretrial and the trial phase as well as to support recruiting children; (5) a longer recruitment period. Consequently, major investments, both financially and in time, are necessary.

But who is willing to pay for this? To date, none of the successful RCTs on monotherapy in children with epilepsy has been completely funded by noncommercial funding organizations. Also, the ILAE recognized that many trials are designed, conducted, and analyzed by pharmaceutical companies and not by independent, unbiased sponsors.[6] Are investigator-initiated RCTs in children with epilepsy not feasible and should we accept off-label prescription for children with epilepsy guided by personal treatment preference? Together with the various initiatives to promote trials in children, we as clinical investigators should make this mission possible. For these independent trials major investments from governmental funding organizations are imperative. We hope higher budgets made available for investigator-initiated RCTs, such as the grants from the National Institute for Health Research for the EcLiPSE study and SANAD II trial, will become rather rule than exception.

ACKNOWLEDGEMENTS

The LEV-VPA study was supported financially by the Netherlands Organisation for Health Research and Development (ZonMW, project number 113202003).
We thank Ms. D.M. Black for editing the text.

REFERENCES

1. Kotsopoulos IA, van Merode T, Kessels FG, et al. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 2002;43:1402-1409.
2. Chung AM and Eiland LS. Use of second-generation antiepileptic drugs in the pediatric population. Paediatr Drugs 2008;10:217-254.
3. Caldwell PH, Murphy SB, Butow PN, et al. Clinical trials in children. Lancet 2004;364:803-811.
4. Klassen TP, Hartling L, Craig JC, et al. Children are not just small adults: The urgent need for high-quality trial evidence in children. PLoS Med 2008;5:e172.
5. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551-563.
6. Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094-1120.
7. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam monotherapy in children with epilepsy: A systematic review. CNS Drugs 2015;29:371-382.
8. Arts WF, Geerts AT, Brouwer OF, et al. The early prognosis of epilepsy in childhood: The prediction of a poor outcome. the dutch study of epilepsy in childhood. Epilepsia 1999;40:726-734.
9. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362:790-799.
10. Strengthening clinical research in children and young people [editorial]. Lancet 2015;385. http://dx.doi.org/10.1016/S0140-6736(15)60974-6.
11. Weijenberg A, Offringa M, Brouwer OF, et al. RCTs with new antiepileptic drugs in children: A systematic review of monotherapy studies and their methodology. Epilepsy Res 2010;91:1-9.
12. Guerreiro MM, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res 1997;27:205-213.
13. Pellock JM, Carman WJ, Thyagarajan V, et al. Efficacy of antiepileptic drugs in adults predicts efficacy in children: A systematic review. Neurology 2012;79:1482-1489.
14. European Parliament. Paediatric regulation L 378. Offical Journal of the European Union 2006;49:1-21.
15. Ruperto N, Eichler I, Herold R, et al. A european network of paediatric research at the european medicines agency (enpr-EMA). Arch Dis Child 2012;97:185-188.
16. Priority Medicines for Children. www.era-learn.eu/network-information/networks/priomedchild
17. Klassen TP, Hartling L, Hamm M, et al. StaR child health: An initiative for RCTs in children. Lancet 2009;374:1310-1312.
18. Amann JP, Glauser T, Chiron C. Developing antiepileptic drugs in children: balancing protection and access. Handb Clin Neurol 2013;111:741-746.
19. Chiron C, Dulac O, Pons G. Antiepileptic drug development in children: Considerations for a revisited strategy. Drugs 2008;68:17-25.
20. Rosenow F, Schade-Brittinger C, Burchardi N, et al. The LaLiMo trial: lamotrigine compared with levetiracetam in the initial 26 weeks of monotherapy for focal and generalised epilepsy--an open-label, prospective, randomised controlled multicenter study. J Neurol Neurosurg Psychiatry 2012;83:1093-1098.
21. Gilliam FG, Veloso F, Bomhof MA, et al. A dose-comparison trial of topiramate as monotherapy in recently diagnosed partial epilepsy. Neurology 2003;60:196-202.
22. Chung S, Ceja H, Gawlowicz J, et al. Levetiracetam extended release conversion to monotherapy for the treatment of patients with partial-onset seizures: a double-blind, randomised, multicentre, historical control study. Epilepsy Res 2012;101:92-102.

23. Ramsay E, Faught E, Krumholz A, et al. Efficacy, tolerability, and safety of rapid initiation of topiramate versus phenytoin in patients with new-onset epilepsy: a randomized double-blind clinical trial. Epilepsia 2010;51:1970-1977.
24. Wheless JW, Neto W, Wang S, et al. Topiramate, carbamazepine, and valproate monotherapy: Double-blind comparison in children with newly diagnosed epilepsy. J Child Neurol 2004;19:135-141.
25. Holmes GL, Frank LM, Sheth RD, et al. Lamotrigine monotherapy for newly diagnosed typical absence seizures in children. Epilepsy Res 2008;82:124-132.
26. Henschel AD, Rothenberger LG, Boos J. Randomized clinical trials in children--ethical and methodological issues. Curr Pharm Des 2010;16:2407-2415.
27. Borggraefe I, Bonfert M, Bast T, et al. Levetiracetam vs. sulthiame in benign epilepsy with centrotemporal spikes in childhood: a double-blinded, randomized, controlled trial (German HEAD study). Eur J Paediatr Neurol 2013;17:507-514.
28. Caldwell PH, Butow PN, Craig JC. Pediatricians' attitudes toward randomized controlled trials involving children. J Pediatr 2002;141:798-803.
29. Anderson M and Choonara I. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. Arch Dis Child 2010;95:731-738.
30. Rheims S, Cucherat M, Arzimanoglou A, et al. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med 2008;5:e166.
31. Modi N, Clark H, Wolfe I, et al. A healthy nation: strengthening child health research in the UK. Lancet 2013;381:73-87.
32. Caldwell PH, Butow PN, Craig JC. Parents' attitudes to children's participation in randomized controlled trials. J Pediatr 2003;142:554-559.
33. Leibson T and Koren G. Informed consent in pediatric research. Paediatr Drugs 2015;17:5-11.
34. Lepola P, Needham A, Mendum J, et al. Informed consent for paediatric clinical trials in europe. Arch Dis Child 2016.

SUPPLEMENTARY DATA

Questionnaire on the feasibility of the LEV-VPA study

You have participated in the LEV-VPA trial. Unfortunately, we had to stop the trial prematurely because the inclusion rate was too low. Herewith, we send you a questionnaire in order to determine why our study was unsuccessful and what we could/should have done differently. We kindly request you to complete the questionnaire and return it to us. Thank you in advance.

1. What were the three most important reasons for you to participate in this trial?
   a. I see many patients for whom I hesitate which antiepileptic drug (AED) is the best to prescribe as first choice
   b. I dislike to prescribe AEDs off-label without evidence of efficacy in the type of patients that I see
   c. I found the research question interesting
   d. I like to cooperate in studies of colleagues
   e. I expected to be able to include many eligible patients
   f. I would like to be co-author of a publication about a study comparing two AEDs
   g. Other, namely

2. What did you think of the amount of oral information you received before the initiation of the study? (Possible answers: enough/too little/too much; explanation)

3. What did you think of the amount of written information you received before the initiation of the study? (Possible answers: enough/too little/too much; explanation)

4. What did you think of the content of the documents in the site file (e.g. protocol, explanation procedures and CRF)? (Possible answers: complete and clear/complete but unclear/ incomplete but clear/incomplete and unclear; explanation)

5. Was it clear in advance what was expected from you in the trial? (Possible answers: yes/no; explanation)

6. Was it clear in advance how much time the study would require per enrolled patient (Possible answers: yes/no; explanation)

7. Did the expectation of time required per enrolled patient meet the reality? (Possible answers: yes/no/ not applicable since I did not enrol patients; explanation)

8. The time required for performing the study was: much less/less/equal to/more/much more than anticipated (explanation)

9. Did you have enough time to perform the study properly? (Possible answers: yes/no; explanation)

10. Did a research nurse participate in this trial? (Possible answers: yes/no)

11. How was the communication with the principal investigator / study coordinator? (Possible answers: the quantity of the contact was good/too little/too much; the quality was good/poor; explanation)

12. How was the communication with the monitor? (Possible answers: the quantity of the contact was good/too little/too much; the quality was good/poor; explanation)

13. Did you include patients? (Possible answers: yes/no (if no, go to question 21))

14. How many patients did you include?

15. How did the randomisation procedure go? (Possible answers: easy/difficult; fast/slow; explanation)

16. How long did it take to receive trial medication after randomisation? (Possible answers: within 1 day/2-4 days/5-7 days/more than 1 week)

17. Was the mentioned time-frame acceptable for you and the patient? (Possible answers: yes/no; explanation)

18. If you included more than one patient: how did the inclusion of subsequent patients go compared to the first patient? (Possible answers: easier/the same/more difficult; explanation)

19. How did completion of the eCRF go the first time? (Possible answers: easy/okay/difficult; took too much time/took acceptable time; explanation)

20. Completion of the eCRF took less/equal/more time after the first time and was easier/harder/just as difficult

21. Did you discuss the study with all eligible patients? (Possible answers: yes/no (if yes, go to question 23))

22. What were possible reasons for not discussing the study with eligible patients? (multiple answers possible)
    a. I assumed that the patient was unwilling to participate
    b. I preferred a certain treatment for certain patients

c. I wanted to start directly with medication without waiting until trial medication had arrived
d. I thought the number of visits for the study was too stressful for the patient
e. I forgot to discuss the trial with the patient
f. The demands of the study withheld me to include patients
g. Other reason, namely

23. What were the most important reasons for not being able to include patients? (multiple answers possible)
    a. Patients were not eligible (which criteria?)
    b. Patients and/or parents did not want to participate
    c. I preferred a certain treatment for certain patients
    d. Immediate start with medication was necessary
    e. Other reason, namely

24. How could inclusion rate have been increased? (multiple answers possible)
    a. The in/exclusion criteria should have been liberalised (example)
    b. I should have had more support from someone in my center
    c. I should have had more support from the study coordinator and/or clinical trials unit
    d. I should have paid more attention to the study and including patients
    e. I should have recruited more actively among e.g. paediatricians in the area
    f. The study better should have been performed in another center/with other professionals (example)
    g. The randomisation procedure should have been changed
    h. The eCRF should have been easier to complete
    i. Other reason, namely

25. Would a financial reimbursement have influenced the number of patients that you included? (Possible answers: yes/no)

26. Are you prepared to participate in a similar trial in the future? (Possible answers: yes/no; explanation)

27. Other remarks

PART B: KETOGENIC DIET

CHAPTER 6

The ketogenic diet: how to act in emergency situations

A. Weijenberg, M. van Rijn, O.F. Brouwer, T.J. de Koning

Adapted from *Praktische Pediatrie number 3, 2017*

BACKGROUND

It is described in the Bible that people suffering from falling disease might well benefit from fasting:

'This kind (people who suffer from falling disease – ed.) can come forth by nothing, but by prayer and fasting.' (Mark 9: 14-29)

In the early 20th century, it became clear that a high-fat diet, the emergence of ketonemia and the positive effect of ketosis on epilepsy were interrelated.[1] Whereas from that time on several antiepileptic drugs (AEDs) were developed, it took a long time for the ketogenic diet (KD) to be reconsidered for the treatment of epilepsy. Since the mid-1990s, however, KD treatment has become a valid treatment option for children with pharmacotherapy-resistant epilepsy. The basic composition of the ketogenic diet is its large percentage of fat in combination with an extremely low percentage of carbohydrates. As a result, fat will become the main energy source, leading to the production of the ketone bodies acetoacetate, b-hydroxybutyrate and acetone. Of these, acetoacetate and b-hydroxybutyrate are able to pass the blood-brain-barrier to replace sugar as primary brain fuel.

Although the underlying mechanisms remain largely unknown, a randomized controlled trial in the UK clearly established the beneficial effect of KD in children with pharmacoresistant epilepsy by showing >50% reduction of seizure frequency in 40% of those on KD compared to 6% of controls.[2] Similar positive results were recently found in a Dutch trial.[3] Apart from a reduction in seizures, other positive effects such as increased energy and alertness levels and the possibility of lowering the dosage of AEDs are frequently reported.

In the classic ketogenic diet a 4:1 or 3:1 ratio grams fat to grams carbohydrates plus protein is used. Variants of the KD, like modified Atkins and KD with added medium chain triglyceride (MCT), have also been proven to be effective.[4] Not only can KD be used in children with pharmacotherapy-resistant epilepsy, but also for certain inborn errors of metabolism such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase deficiency.

Treatment with KD generally takes place in university hospitals or specialized epilepsy centers where both international[5] and national (*Zorgpad Ketogeen dieet behandeling bij refractaire epilepsie & metabole ziekten bij kinderen)*[6] recommendations serve as important guidelines. In the Netherlands, the KD is initiated in about 70 children each year. It is therefore not unlikely for general pediatricians to come across children on KD. As their metabolic changes are considerable and carbohydrates in their foods are extremely limited, a special and individual emergency protocol is needed for these children. Normally, intravenous fluids for children contain glucose/saline solutions. However, any carbohydrate taken will immediately suppress the burning of fat (and the production of ketone bodies) and may lead to increase of seizures with even status epilepticus as a possible outcome.[5] The importance of such an emergency protocol is illustrated by the following case.

Case presentation

An 11-year-old boy with pharmacotherapy-resistant frontal lobe epilepsy has been on KD treatment for 1.5 years. Both patient and parents are satisfied by the effect of the KD. Although the KD is very strict, the advantages outweigh the disadvantages. His seizure frequency has decreased and there is less need for emergency medication. He even feels much more energetic during daytime, which has improved his participation both at home and at school.

In spite of stable and adequate ketosis (5.4 mmol/L measured in blood the night before), and regular intake of his antiepileptic drugs in the previous days, he presents to the emergency department of the nearest general hospital with clusters of seizures that failed to respond to regular emergency medication, midazolam nasal spray.

Intermezzo

Considering the clinical condition of ongoing clusters of seizures in a hemodynamically stable boy who is being treated with antiepileptic drugs and who is also on KD, what action is required to get into control of the situation again? Which aspects are of major importance? Which parameters and checks must be set?

When taking care of a patient with progressive increase of seizure activity while being on a KD, possible metabolic disturbances such as hypoglycemia and ketoacidosis should be considered carefully. Therefore, after assessing and monitoring vital signs, assessment and treatment should focus on the epilepsy as well as on the metabolic situation.

Case (continued)

In this boy initial treatment consists of maintenance infusion of 0.1 mg/kg/h midazolam. Because of unsuccessful seizure control, a loading dose of fenytoin 20 mg/kg is administered intravenously, later followed by another 10 mg/kg. Because the seizures persist, it is decided to give another bolus of midazolam intravenously, followed by an increased maintenance dose of midazolam. At that moment the patient is intubated and transferred to the pediatric intensive care unit of a university hospital. On arrival there, blood ketone concentration is 1.5 mmol/L (normal range for adequate ketosis 2.5-5.5 mmol/L). Serum glucose is in the normal range and patient has no fever. A few hours later, seizures are controlled and midazolam dosage can be tapered down. Soon after, he can be extubated and KD is restarted by means of tube feeding. After several days, ketosis is adequate, the feeding tube is removed, the patient restarts his normal KD regimen and he is able to leave the hospital again.

Emergency treatment protocol for children on ketogenic diet

Any child on KD should have an emergency treatment protocol including the steps that should be taken in case of a metabolic derangement or hospital admission for whatever reason. This individual emergency protocol is based among other things on the total amount of grams carbohydrates per day the child is allowed to take, which is different for each patient.

The first steps can be taken at home. In case of symptomatic hypoglycemia or a blood glucose level below 2.6 mmol/L, parents should give 30 to 60 ml fruit juice depending on the child's weight. In case of symptomatic hyperketonemia (5.0-6.5 mmol/L) or a blood ketones concentration above 6.5 mmol/L, again fruit juice is given by the parents. An alternative to fruit juice would be the equivalent of 3 to 6 grams carbohydrates for which a maltodextrin like Fantomaltâ can be used. Given the fact that the daily permitted amount of grams carbohydrates is very limited, the amount of fruit juice that must be used as a first step in case of (a likely) derangement should be kept to a minimum. Fever may induce ketosis as well as ketoacidosis. Therefore, fever reducing measures and medicines are usually indicated. In case of nutritional issues or gastrointestinal disturbances, the food amounts of the KD need to be reduced temporarily while keeping up the ratio fat to carbohydrates plus protein. If recovery is insufficient, the emergency treatment has to be continued clinically.

The emergency treatment protocol for children on KD should not be confused with the emergency procedure in case of a status epilepticus, for which each child has a specific epilepsy treatment protocol. The two protocols should be used alongside each other.

At the emergency department, initial clinical assessment must take place, followed by measurement of the blood ketone and glucose levels (the patient's own ketone- and glucose indicator may be used). Whether tube feeding or rehydration by intravenous infusion is started depends on the level of dehydration, presence of nutritional problems, level of ketosis, blood glucose level, type of epilepsy and other potential underlying provoking factors. Initially, children on KD will generally start with normal saline intravenously only, with the daily permitted amount of carbohydrates added. This implies that these children will receive infusion fluids that contain significantly lower concentrations of glucose than usually. It also implies a deviation from the APLS guideline for the treatment of hypoglycemia (25-50 ml glucose 10% depending on weight). Furthermore, particular attention must be paid to the fact that medication, especially liquid formulations and laxatives, will most likely contain considerable amounts of carbohydrates that should be included in the total amount of carbohydrates that is allowed daily. Consultation of the hospital pharmacist at an early stage for calculation of the amount of carbohydrates in medication is advisable. If the medical condition still does not improve, the above mentioned steps should be repeated and the pediatric specialist in metabolic diseases involved in the KD treatment must be consulted. With the help of the pediatric neurologist, the treating pediatrician may advise on the next steps and take over the treatment if necessary.

If a child has been admitted to the hospital because of a general pediatric condition, the emergency treatment protocol for children on KD will cover guidelines concerning infusions and monitoring, also in case of anesthesia. In such cases the KD team should be accessible at all times.

DISCUSSION

In our patient, treatment of the frequent seizures was given priority at the emergency department of the general hospital. However, he did not actually have status epilepticus and was hemodynamically stable. Measurement of blood ketones and glucose should have taken place at initial assessment for two reasons. First, derangement of ketones and/or glucose may provoke seizures and treatment should be adapted if necessary. Second, it is important to have a reference level as a starting point and to keep the patient in adequate ketosis. It is well-known that low ketone levels in children on KD for some time can lead to a serious increase of seizures. Another aspect that deserved more attention is the kind of infusion fluids the patient received. It is not unlikely that a glucose/saline infusion was given.

It is unknown whether the decrease of blood ketone level from 5.4 mmol/L to 1.5 mmol/L provoked the exacerbation of seizure activity. Our patient never had such an increase of seizure activity before while on KD.

CONCLUSION

Even though KD treatment generally takes place in university hospitals and specialized epilepsy centers, children treated with KD may also present at the emergency unit of a general hospital. Reasons may be an increase of seizures, a metabolic derangement (ketoacidosis or hypoglycemia) or a more general pediatric condition. General pediatricians must be able to give these children adequate acute care always keeping in mind some important aspects:

- to measure blood ketones and glucose, as well as arterial blood gas at initial assessment;
- to start the patient on a normal saline only infusion;
- to take into account that medication may contain carbohydrates;
- and to act according to the emergency protocol which all parents have at their disposal (and which the nearest general hospital should have access to and be familiar with).

Finally, the pediatric metabolic disease expert who is involved in KD therapy should be consulted about the next steps.

ACKNOWLEDGEMENTS

The authors thank Coriene Catsman-Berrevoets, Danielle Lambrechts, and Michèl Willemsen for reviewing the manuscript.

REFERENCES

1. Wilder RM. High fat diets in epilepsy. Mayo Clin Bull 1921;2:308.
2. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500-506.
3. Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand 2017;135:231-239.
4. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 2009;50:1109-1117.
5. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia 2009;50:304-317.
6. Louw EJTM, Hurk TAM, Catsman-Berrevoets CE, et al. Zorgpad ketogeen dieet behandeling bij refractaire epilepsie & metabole ziekten bij kinderen. https://www.stofwisselingsziekten.nl/zorgpad-ketogeen-dieet-vernieuwd/

CHAPTER 7

Ketogenic diet in refractory childhood epilepsy: starting with a liquid formulation in an outpatient setting

A. Weijenberg, M. van Rijn, P.M.C. Callenbach, T.J. de Koning, O.F. Brouwer

Child Neurology Open 2018;5:1-7

ABSTRACT

Background

Ketogenic diet in children with epilepsy has a considerable impact on daily life and is usually adopted for at least 3 months. Our aim was to evaluate whether the introduction of an all-liquid ketogenic diet in an outpatient setting is feasible, and if an earlier assessment of its efficacy can be achieved.

Methods

The authors conducted a prospective, observational study in a consecutive group of children with refractory epilepsy aged 2 to 14 years indicated for ketogenic diet. Ketogenic diet was started as an all-liquid formulation of the classical ketogenic diet, KetoCal 4:1 LQ, taken orally or by tube. After 6 weeks, the liquid diet was converted into solid meals. The primary outcome parameter was time-to-response (>50% seizure reduction). Secondary outcome parameters were time to achieve stable ketosis, the number of children showing a positive response, and the retention rate at 26 weeks.

Results

Sixteen children were included. Four of them responded well with respect to seizure frequency, the median time-to-response was 14 days (range 7-28 days). The mean time to achieve stable ketosis was 7 days. The retention rate at 26 weeks was 50%. Of the 8 children who started this protocol orally fed, 6 completed it without requiring a nasogastric tube.

Conclusions

Introduction of ketogenic diet with a liquid formulation can be accomplished in orally fed children without major complications. It allowed for fast and stable ketosis.

INTRODUCTION

The ketogenic diet is a high fat, very low-carbohydrate diet. It has become one of the nonpharmacological treatment options for children with medical refractory epilepsy, although its mechanism of action is still unclear.[1] The metabolism of a high amount of dietary fat means that ketone bodies become the main energy source for the whole body and brain. The efficacy of the classical ketogenic diet for children with refractory epilepsy has been strongly supported by 2 randomized controlled trials.[2, 3] For children with glucose transporter type 1 deficiency or pyruvate dehydrogenase complex deficiency, ketogenic diet is the treatment of first choice.[4]

The classical ketogenic diet consists of dietary long-chain triglycerides and is based on a ratio of 3:1 or 4:1 (fat:[carbohydrate + protein]). Consequently, the amount of carbohydrate is very restricted and the amount of protein is minimal, which could have a negative influence on physical growth.[5] A ketogenic diet variant with medium-chain triglycerides allows a higher intake of carbohydrates and protein, since medium-chain triglycerides produces more ketones per kilocalorie of energy than long-chain triglycerides. This less restrictive medium-chain triglycerides seems as effective as the classical ketogenic diet.[6] However, both the taste of medium-chain triglycerides oil and associated gastrointestinal complaints may compromise the intake.

In clinical practice, the mean time period for adopting the ketogenic diet before considering its continuation/discontinuation because of inefficacy is 3.5 months.[7] A rapid assessment of its efficacy is highly desirable because of the significant impact of the ketogenic diet on the child and his or her caretakers.

Introducing an all-liquid diet requires less complicated instructions than regular and very strict ketogenic diet meals. The implementation of a liquid diet can be much easier for parents or caretakers and ensures a more stable intake with a minimal risk of mistakes. The authors hypothesized that the use of an all-liquid formulation might contribute to an earlier and more stable metabolic situation and level of ketosis, making earlier assessment of efficacy possible. The authors aimed to investigate the feasibility of introducing an all-liquid formulation of ketogenic diet in children with refractory epilepsy and to evaluate whether its efficacy could be assessed reliably within 6 weeks.

MATERIALS AND METHODS

Patients

This prospective study was carried out in the Beatrix Children's Hospital of the University Medical Center of Groningen, the Netherlands, between 2013 and 2016. All children, aged between 2 and 11 years (oral feeding) or aged between 2 and 14 years (tube feeding), who were referred for ketogenic diet treatment because of refractory epilepsy and who fulfilled predefined inclusion and exclusion criteria according to the Recommendations of the International Ketogenic Diet Study Group[7] could be included. Refractory epilepsy was defined as inadequate seizure control despite treatment with at least 2 antiepileptic drugs in an optimal dose.[8] Treatment with vagus nerve stimulation was not considered as an exclusion criterion.

Ketogenic diet and procedures

Ketogenic diet was started in small groups of 2 to 4 children at the same time. After a joint information meeting with the parents and the ketogenic diet team, baseline investigations were performed, including blood and urine tests, electroencephalography, electrocardiography, renal ultrasound, bone mineral density scan, nutritional evaluation, and evaluation of their medication. During this prephase, individual instructions about the ketogenic diet were given to the parents and, if possible, to their child. If there were no contraindications and parents agreed to start with an all-liquid formulation, ketogenic diet was started without an initial fasting period in an outpatient setting. The diet comprised an all-liquid formulation (KetoCal 4:1 LQ) taken orally or by tube with a 10-day, stepwise conversion into a classical liquid ketogenic diet, with a ratio 4:1 of fat:(carbohydrate + protein). A slower introduction was allowed on an individual basis. KetoCal 4:1 LQ could be mixed with carbohydrate-free flavors. All children who could tolerate oral feedings were allowed to have a low-carbohydrate snack, like a piece of cucumber, once or twice a day. Levels of ketosis and glucose were measured in capillary blood samples twice a day (morning and evening) during the first 2 weeks and thereafter once a week and when indicated.

After the introductory phase of 6 weeks, the classical, liquid ketogenic diet was converted into a diet consisting of meals combined with both long-chain triglycerides (KetoCal 4:1 LQ and/or oral dietary products) and medium-chain triglycerides, allowing more protein and carbohydrates to be consumed. The content of the diet was adjusted to calculated percentages of total energy, initially aiming for a distribution of medium-chain triglycerides 43%, long-chain triglycerides 35%, protein 12%, and carbohydrate 10%. Fine-tuning of the diet was based on tolerability, level of ketosis, growth, and individual needs and preferences. During this transition phase, ketosis was measured daily in the evening, until it had again stabilized. Children were seen in the outpatient clinic every 2 weeks during the introductory phase and then regularly until 52 weeks after the start of the all-liquid ketogenic diet.

The study was performed according to the guidelines of the University Medical Center Groningen's medical ethics committee. Since ketogenic diet is part of the regular treatment options for children

with pharmacologically resistant epilepsy, the ethics committee did not need to make a formal assessment of this observational study.

Outcomes

Parents and children were asked to keep a diary, including a 4-week baseline period, before the start of the ketogenic diet. The diary included items like seizure type and frequency, use of emergency medication, levels of ketosis and blood glucose, adverse events with special attention for constipation and vomiting, and other individual details when applicable. Changes in antiepileptic drugs during the first 6 weeks were allowed only if they were considered really necessary and these had to be recorded in the diary too.

The primary outcome parameter was time-to-response, defined as time to the first day of a period of at least 7 consecutive days with >50% seizure reduction compared to the seizure frequency before the start of ketogenic diet. Secondary outcome parameters were time to achieve stable ketosis (defined as ≥2.5 mmol/L in blood for at least 2 days); the number of children showing a positive response (responder rate) at 6, 12, and 26 weeks; the retention rate at 26 weeks; and the reasons for discontinuation of ketogenic diet.

RESULTS

Patients

Between April 2013 and January 2016, a liquid ketogenic diet was initiated in 16 children. Their clinical characteristics are shown in Table 1. In 10 of 16 children, the seizure frequency was uncountable before the start of ketogenic diet or seizures could not be adequately registered by the parents (difficult to interpret, inconsistent presentation). All children except 1 had multiple seizures types.

Efficacy and tolerability

Table 2 shows the primary and secondary outcome parameters together with the main aspects concerning tolerability. Only 4 of the 16 children responded well in relation to their seizure frequency, with all of them achieving a response within 4 weeks after the start of the ketogenic diet (Table 2). There were no further responders after 6 weeks. Follow-up time was at least 1 year. The mean time taken to achieve stable ketosis was 7 days (15/16 children). One child never reached the desired level of ketosis (≥2.5 mmol/L). Not only the 4 responders stayed on the diet after the 6-week introductory phase; 8 children did so for at least 26 weeks (ie, the retention rate at 26 weeks was 50%, both in orally fed and tube-fed children). Apart from reduction in seizure frequency, additional reasons for continuing ketogenic diet, as reported by the parents in their diaries, were changes in seizure type (shorter and/or less severe seizures); less need for emergency medication;

Table 2. Efficacy and tolerability of KD

Patient	Responder[a]	Time-to-response (days)	Time to stable ketosis (days)	Level of ketosis[b] (mmol/L)	Duration KD (weeks)	KD at 26 weeks	KD at 52 weeks	Constipation	Admission to hospital (0-6 weeks)
1	Yes	28	8	2.6 – 4.0	49	Yes	No	No	No
2	No	NA	2	2.1 – 5.9	14	No	No	Yes	No
3	Yes	15	7	2.2 – 5.4	>65[c]	Yes	Yes	Yes	No
4	No	NA	7	2.7 – 4.9	7	No	No	Yes	No
5	No	NA	7	2.7 – 5.9	97	Yes	Yes	No	No
6	No	NA	13	2.7 – 5.9	>165[c]	Yes	Yes	No	No
7	No	NA	1	3.5 – 5.3	11	No	No	Yes	Beforehand
8	Yes	7	6	3.3 – 4.6	>203[c]	Yes	Yes	Yes	No
9	No	NA	NA	0.7 – 1.9	17	No	No	Yes	No
10	No	NA	2	2.4 – 5.3	15	No	No	Yes	Yes
11	No	NA	6	2.4 – 5.4	19	No	No	No	No
12	No	NA	20	1.1 – 5.5	41	Yes	No	No	No
13	No	NA	11	2.7 – 5.5	9	No	No	No	No
14	No	NA	5	2.8 – 5.2	26	Yes	No	Yes	No
15	Yes	14	5	2.6 – 5.0	>141[c]	Yes	Yes	No	Yes
16	No	NA	4	1.9 – 3.6	12	No	No	Yes	No

[a] Response was defined as >50% seizure reduction.
[b] Level of ketosis week 3 to 6: 10-90 percentiles
[c] Still continuing KD in April 2017
KD, ketogenic diet; NA, not applicable

and improvement of alertness, cognitive functioning (eg, starting to speak words again, walking again), and/or physical well-being (eg, being able to go to school every day).

In the 8 children who stopped ketogenic diet after 6 weeks, the reasons for discontinuing the diet were inefficacy and/or lack of other benefits, which did not outweigh the burden of the diet. There were no changes to their antiepileptic drug regimens during the first 6 weeks.

Generally, the ketogenic diet was well tolerated. Constipation, the most common adverse event, could be easily controlled by laxatives. Two children needed a high enema during the introductory phase. None of the children experienced an increase in vomiting or other gastrointestinal problems. Introducing the ketogenic diet in an outpatient setting was found to be safe; 2 children had 1 or 2 episodes with vomiting, most likely due to high ketosis (maximums of 5.6 and 7.6 mmol/L) combined with hypoglycemia (1.4 and 2.0 mmol/L, respectively) in the first week, for which they were seen in hospital and could easily be controlled with extra carbohydrates. It appeared that in one of these children, the ketogenic diet had been introduced too rapidly by the mother (within 2 days) instead of using the stepwise instructions for the ketogenic diet. One child, who was electively hospitalized before the start of ketogenic diet for social reasons, had unexplained high ketosis (maximum 6.6 mmol/L) in the first week without further symptoms and with normal blood glucose, which could be corrected with extra carbohydrates.

Ketogenic Diet: All-liquid introduction and transition to meals

Half of the children were already being tube-fed before ketogenic diet was initiated. For these children and their parents initiating ketogenic diet with an all-liquid formulation was relatively simple. The remaining 8 children were also started with a complete liquid ketogenic diet although they were allowed to replace the liquid formula by an equivalent amount of KetoCal 4:1 LQ as a muffin or pancake based on the Ketocal 4:1 powder, if liquid intake only became problematic. This was only done incidentally. In addition, they were also allowed to have a low-carbohydrate chewable snack, such as a piece of cucumber. Two children received a nasogastric tube temporarily during the first weeks of the introductory phase: one child, known with behavioral problems, because of difficult intake of the KetoCal 4:1 LQ, the other because of insufficient dietary intake before initiating the ketogenic diet. The latter received a percutaneous endoscopic gastrostomy (tube) after discontinuation of ketogenic diet. During the introductory phase all the children maintained a stable bodyweight. After the conversion to solid meals, 5 of the 6 children without a tube continued using KetoCal 4:1 LQ in their diet for at least another 6 weeks, in combination with oral food preparations and medium-chain triglycerides. For the tube-fed children, the ketogenic diet was adapted by adding medium-chain triglycerides and increasing the amount of protein given. The characteristics of the ketogenic diet during the introductory phase (classical ketogenic diet at 4 weeks) and after the transition to meals (variant with medium-chain triglycerides at 12 weeks) for each patient are shown in Table 3. In 2 children who were totally tube-fed, the classical ketogenic diet was not adapted after 6 weeks because of other severe health problems.

Table 1. Demography and clinical characteristics

Patient/ Gender	Age at onset epilepsy (years; months)	Age at KD initiation (years; months)	Number of AEDs[a]	Main seizure type	Epilepsy type/ epilepsy syndrome	Etiology	Seizure frequency[a] (per month)	Intellectual Impairment
1/M	1;2	1;11	3	Epileptic spasms	West syndrome	Unknown	Uncountable[b]	Severe
2/M	0;1	4;8	3	Focal motor	Multifocal	Unknown[c]	30	Severe
3/F	0;3	3;2	3	Focal motor	Focal	Unknown	30	Moderate
4/F	0;3	2;0	3	Epileptic spasms	West syndrome	Lissencephaly (LIS1-mutation)	Uncountable	Severe
5/M	6;1	11;7	3	Focal motor	Focal	KCNT1-mutation	50	Moderate
6/M	0;7	3;5	4	Atypical absences	Generalized	Angelman syndrome (15q11.2q12 deletion)	Uncountable	Severe
7/F	0;1	6;6	2	Generalized tonic-clonic	Multifocal	Unknown	Uncountable	Moderate
8/M	0;4	7;1	3	Focal nonmotor	Focal	Structural lesion after intracerebral hemorrhage	12	Moderate
9/M	2;0	7;7	4	Generalized tonic	Lennox Gastaut	Microcephaly with simplified gyral pattern and double cortex	Uncountable	Severe
10/M	1;0	6;1	1	Generalized tonic-clonic	Multifocal	Unknown	Uncountable	Severe
11/F	0;0	3;0	1†	Focal motor	Multifocal	Structural lesion after postnatal hypoglycemia	Uncountable	Severe
12/M	7;9	9;0	4	Generalized tonic	Multifocal	Post HSV encephalitis anti-NMDA receptor encephalopathy	Uncountable	Severe
13/M	10;9	14;11	3	Focal motor	Multifocal	Cri du Chat syndrome (5p deletion and 4q deletion)	65	Severe
14/F	1;8	2;5	2	Generalized atonic	Lennox Gastaut	Unknown	Uncountable	Severe
15/M	4;0	6;2	0	Focal motor	NA[e]	Glucose transporter type 1 deficiency (SLC2A1-mutation)	<1	Mild
16/F	0;7	3;3	4	Generalized tonic-clonic	Lennox Gastaut[f]	Lobar holoprosencephaly	Uncountable	Severe

[a] Number of AEDs and seizures at KD initiation, respectively
[b] Uncountable = seizure frequency was too high to count or seizures could not be accurately registered (too difficult to interpret, unreliable presentation)
[c] Brother died of Mitochondrial DNA depletion syndrome (mtDNA depletion syndrome)
[d] Tapering off of 1 of 2 AEDs started before the introduction of KD and was withdrawn 4 weeks after starting KD
[e] Uncertain whether attacks were of epileptic origin
[f] Without typical EEG correlation
AEDs, antiepileptic drugs; EEG, electroencephalopathy; HSV, herpes simplex virus; KD, ketogenic diet; NA, not applicable; NMDA, N-methyl-D-aspartate

Table 3. Dietary characteristics

Patient	Tube	Weight at 4 weeks (kg)	BMI at 4 weeks (SD)	Protein at 4 weeks (g/kgbw)	Protein at 12 weeks (g/kgbw)	Fat at 12 weeks (g/kgbw)	MCT:total fat at 12 weeks (%)
1	Yes	12.0	-0.13	1.5	1.5	6.3	0[a]
2	Yes	16.4	-1.00	1.5	1.5	6.6	30.3
3	Yes	14.2	+1.13	1.8	2.2	6.0	11.8
4	Yes	13.8	+0.50	1.6	NA	NA	NA
5	No	37.8	-0.35	1.0	1.4	6.1	31.9
6	Yes	16.0	-1.41	1.3	1.9	5.8	0[b]
7	No[c]	18.4	+0.03	1.3	2.1	5.6	47.1
8	No	23.9	-0.19	1.5	1.9	7.2	43.6
9	No	26.5	+0.24	1.1	1.7	6.7	33.0
10	No[c]	21.0	-0.81	1.5	1.8	6.4	26.7
11	No	16.9	-0.03	1.5	1.9	7.0	41.5
12	Yes	26.8	+0.21	1.4	1.4	6.5	0[a]
13	Yes	39.7	-1.21	1.0	NA	NA	NA
14	No	15.5	+1.81	1.4	2	5.4	26.1
15	No	22.2	+0.76	1.5	2.5	5.2	37.9
16	Yes	16.5	+1.71	0.9	1.4	3.9	0[b]

[a] Classical KD.
[b] Very low energy intake.
[c] Patients 7 and 10 needed a tube during the introduction phase.
BMI, body mass index; KD, ketogenic diet; kg, kilogram; kgbw, kilogram bodyweight; MCT, medium-chain triglyceride; NA, not applicable; SD, standard deviation (based on age).

DISCUSSION

Our study shows that introduction of ketogenic diet with a liquid formulation in an outpatient setting is feasible and contributes to achieving a rapid and stable ketosis. Only 1 child did not achieve stable ketosis, which was probably due to noncompliance. In all the children who had a >50% decrease of seizure frequency, time-to-response was less than 4 weeks. Our study therefore supports the idea that it is possible to evaluate the efficacy of this type of ketogenic diet within 6 weeks. This is in line with others who have concluded that most children who show a positive effect on ketogenic diet have a seizure reduction within the first 2 weeks and that it is reasonable to discontinue the ketogenic diet if it did not result in a seizure reduction after 8 weeks.[9] Although individual choices exist, most parents are counselled to continue the ketogenic diet, even if apparently ineffective, for at least 3 months as recommended by the International Ketogenic Diet Study Group.[7] More studies are needed to support that efficacy of the ketogenic diet with solid foods can be evaluated within 6 weeks.

Introducing the ketogenic diet with this all-liquid formulation, KetoCal 4:1 LQ, was simple, minimizing potential dietary errors and with a mean time period of less than 7 days to achieve stable ketosis. In particular, for children who were already tube-fed and for those in an intensive care setting, a liquid diet can be beneficial.[10, 11] Also for children who are reluctant to eat ketogenic diet, a liquid ketogenic diet using a formula-based powder is a good alternative.[12] In general, it was well accepted by parents and children. None of the parents or children decided to discontinue or change the diet because of the all-liquid formulation. The intention was to start and stay all-liquid for 6 weeks, but incidentally children were allowed to eat a muffin or pancake based on the Ketocal 4:1 powder, instead of the equivalent amount of KetoCal 4:1 LQ. This happened only sporadically and the risk for dietary errors by allowing this muffin was negligibly small. The level of ketosis in these children remained stable. During the transition to ketogenic meals after 6 weeks, the ketosis in the children became less stable and it took some time to personalize the diet with medium-chain triglycerides and reach stable ketosis again. This did not cause an increase of seizure frequency or a decrease in well-being during this period.

An all-liquid, ready-to-use ketogenic diet formulation including medium-chain triglycerides not yet available commercially. This makes the transition from the all-liquid phase to solid meals more complicated if a diet with medium-chain triglycerides and more protein is preferred. In total, the dietician's time investment was about the same as that for children who immediately started treatment with a variant of the ketogenic diet with meals, but the transition for children and parents/caretakers was split into easier to manage steps: first adjusting to following a strict diet and monitoring blood values, and later on learning to prepare solid meals with the ingredients permitted.

The responder rate in our study was 25%. This included 1 child with a glucose transporter type 1 deficiency, which is generally known to respond well to ketogenic diet. Our responder rate is lower than the response rate of 38 to 50% reported in 2 randomized controlled trials.[2, 3] The most likely

explanation for this is the severity of the children's epilepsy in our study, which seems obvious when looking at their seizure frequencies. In 10 of 16 children, the seizure frequency could even not be determined because the seizures were uncountable, many of the seizures were too difficult to interpret for parents, or seizures went unnoticed. A limitation of our study was the absence of a control group on regular ketogenic diet for comparing responder rate.

The retention rate at 26 weeks of 50% suggests that also other aspects are considered important in the decision to continue ketogenic diet. Some of those are quite subjective, in particular those regarding the child's well-being, and were not formally tested. Retention rate has been suggested as a more useful outcome parameter than the >50% reduction of seizure frequency, which is especially true for children with many or even uncountable seizures.[13,14,15] Retention rate combines efficacy and tolerability, but also perceived improvement in activities of daily living and quality of life. It also reflects the impact of a diet on the patient and family's daily life.

Constipation was the most common adverse event of the ketogenic diet, occurring in 9 of 16 children; it is a well-known complication of the diet. We did not observe any other gastrointestinal symptoms such as vomiting and diarrhea.[16] Constipation was mostly solved by adding laxatives. The 2 children who needed enemas during the introductory phase had already dealt with persistent constipation before the ketogenic diet introduction. All parents experienced being able to perform the introduction at home as an advantage of our treatment protocol. More importantly, the introduction at home proved to be safe. Initiating ketogenic diet in an outpatient setting is becoming more common and is also standard care in another ketogenic diet center in the Netherlands.[17]

One of the long-term concerns of the classical ketogenic diet is its negative effect on physical growth due to its limited protein content.[5] The ketogenic diet variant with medium-chain triglycerides has the advantage of allowing a higher amount of protein and carbohydrates compared to the classical ketogenic diet (Table 3). Still, no significant differences in growth were found between the classical and medium-chain triglycerides diet groups after 12 months, despite the significantly higher protein intake in the medium-chain triglycerides diet.[5] In our ketogenic diet with medium-chain triglycerides, we prescribed even more protein than Neal et al.[5] – with a mean content of 1.86 g/kg compared to 1.67 g/kg. In our study, the growth rates were within normal limits for the children who were on the ketogenic diet for more than 6 months (n = 8) or more than a year (n = 5), except for 1 child whose growth was stable at 1 standard deviation below his original growth curve.

CONCLUSION

Our results suggest that introduction of ketogenic diet with a liquid formulation is feasible, with good tolerability and acceptance, and the diet can be safely introduced in an outpatient setting. It can be easily applied in tube-fed children but is also a good alternative for insecure parents or in difficult social situations. The mean time to achieving stable ketosis was within 7 days, with a median time-to-response of 2 weeks. Early stable ketosis and a short time period to response made it possible to assess the ketogenic diet's efficacy within 6 weeks, which is an advantage as well. Although the positive response rate was low (4/16), the parents of another 4 children were satisfied with the diet because it led to less severe seizures or improved well-being, which resulted in a retention rate of 50% after 6 months.

DISCLOSURE

This was an investigator initiated study which was financially supported by Nutricia. The sponsor had no part in data collection, analysis, interpretation, and/or writing the report. Ketocal LQ was provided by a commercial company (not Nutricia) and reimbursed by the health care provider.

ACKNOWLEDGEMENT

We thank Jackie Senior for editing the manuscript.

The Dutch Epilepsy Foundation financially supported a pilot study titled *Biochemical implications of ketogenic diet in children with epilepsy: a pilot study using a metabolomics approach* (WAR 11-06) (not published in this thesis).

REFERENCES

1. Hartman AL, Gasior M, Vining EP, et al. The neuropharmacology of the ketogenic diet. Pediatr Neurol 2007;36:281-292.
2. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500-506.
3. Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand 2017;135:231-239.
4. Scholl-Burgi S, Holler A, Pichler K, et al. Ketogenic diets in patients with inherited metabolic disorders. J Inherit Metab Dis 2015;38:765-773.
5. Neal EG, Chaffe HM, Edwards N, et al. Growth of children on classical and medium-chain triglyceride ketogenic diets. Pediatrics 2008;122:e334-40.
6. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 2009;50:1109-1117.
7. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia 2009;50:304-317.
8. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51:1069-1077.
9. Kossoff EH, Laux LC, Blackford R, et al. When do seizures usually improve with the ketogenic diet? Epilepsia 2008;49:329-333.
10. Hosain SA, La Vega-Talbott M, Solomon GE. Ketogenic diet in pediatric epilepsy patients with gastrostomy feeding. Pediatr Neurol 2005;32:81-83.
11. Kossoff EH, McGrogan JR, Freeman JM. Benefits of an all-liquid ketogenic diet. Epilepsia 2004;45:1163.
12. Ashrafi MR, Hosseini SA, Zamani GR, et al. The efficacy of the ketogenic diet in infants and young children with refractory epilepsies using a formula-based powder. Acta Neurol Belg 2017;117:175-182.
13. Ben-Menachem E, Sander JW, Privitera M, et al. Measuring outcomes of treatment with antiepileptic drugs in clinical trials. Epilepsy Behav 2010;18:24-30.
14. Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094-1120.
15. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551-563.
16. Martin K, Jackson CF, Levy RG, et al. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev 2016;2:CD001903.
17. Vehmeijer FO, van der Louw EJ, Arts WF, et al. Can we predict efficacy of the ketogenic diet in children with refractory epilepsy? Eur J Paediatr Neurol 2015;19:701-705

CHAPTER 8

The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study

A. Weijenberg*, M. E. van Egmond*, M. van Rijn, J.W.J. Elting, J. Gelauff, R. Zutt, D.A. Sival, R.A. Lambrechts, M.A. J. Tijssen, O.F. Brouwer, T.J. de Koning

*Equal contributors

Orphanet Journal of Rare Diseases 2017; 12:45

ABSTRACT

Background

North Sea Progressive Myoclonus Epilepsy is a rare and severe disorder caused by mutations in the *GOSR2* gene. It is clinically characterized by progressive myoclonus, seizures, early-onset ataxia and areflexia. As in other progressive myoclonus epilepsies, the efficacy of antiepileptic drugs is disappointingly limited in North Sea Progressive Myoclonus Epilepsy. The ketogenic diet and the less restrictive modified Atkins diet have been proven to be effective in other drug-resistant epilepsy syndromes, including those with myoclonic seizures. Our aim was to evaluate the efficacy of the modified Atkins diet in patients with North Sea Progressive Myoclonus Epilepsy.

Results

Four North Sea Progressive Myoclonus Epilepsy patients (aged 7-20 years) participated in an observational, prospective, open-label study on the efficacy of the modified Atkins diet. Several clinical parameters were assessed at baseline and again after participants had been on the diet for 3 months. The primary outcome measure was health-related quality of life, with seizure frequency and blinded rated myoclonus severity as secondary outcome measures.

Ketosis was achieved within 2 weeks and all patients completed the 3 months on the modified Atkins diet. The diet was well tolerated by all four patients. Health-related quality of life improved considerably in one patient and showed sustained improvement during long-term follow-up, despite the progressive nature of the disorder. Health-related quality of life remained broadly unchanged in the other three patients and they did not continue the diet. Seizure frequency remained stable and blinded rating of their myoclonus showed improvement, albeit modest, in all patients.

Conclusions

This observational, prospective study shows that some North Sea Progressive Myoclonus Epilepsy patients may benefit from the modified Atkins diet with sustained health-related quality of life improvement. Not all our patients continued on the diet, but nonetheless we show that the modified Atkins diet might be considered as a possible treatment in this devastating disorder.

BACKGROUND

North Sea Progressive Myoclonus Epilepsy (NSPME) is a rare but devastating disorder clinically characterized by progressive myoclonus, seizures, early-onset ataxia and areflexia. In the great majority of patients NSPME is caused by the same homozygous c.430G > T (p.Gly144Trp) mutation in the *GOSR2* gene, first reported in 2011.[1] In 2013 Boissé Lomax and colleagues coined the term NSPME, as all the patients described came from countries bounding the North Sea.[2]

The clinical picture of NSPME is dominated by spontaneous and action-induced myoclonic jerks and ataxia, which have a severe impact on daily functioning.[3] Most NSPME patients also have generalized tonic or tonic-clonic seizures, albeit that the seizures are relatively mild compared to the myoclonic jerks. Both myoclonic jerks and seizures can be treated with anti-epileptic drugs, but the benefits are disappointingly limited. Progressive myoclonic epilepsies, as a group, are not amenable to epilepsy surgery.[4] Vagus nerve stimulation can lead to seizure reduction, but does not help control the myoclonus.[5] This absence of an effective treatment for NSPME served as an impetus for exploring alternative treatment options.

The ketogenic diet (KD) has been proven to be effective in other drug-resistant epilepsy syndromes[6, 7], including those with myoclonic seizures.[8, 9] The modified Atkins diet (MAD) is a less restrictive variant of the classical KD and has shown similar benefits in seizure disorders.[10] The KD is a high-fat, low-carbohydrate diet. In contrast to the classical KD, the MAD does not restrict protein- or calorie-intake. The MAD is therefore easier to maintain, facilitating long-term compliance, especially in adolescents and young adults.[11]

Our aim was to evaluate the efficacy of the MAD in patients with NSPME by measuring health-related quality of life (HRQL) as the primary outcome.

METHODS

Participants

Four NSPME patients aged between 7 and 20 years, all with the known c.430G > T (p.Gly144Trp) mutation, participated in an observational, prospective, open-label study on the efficacy of the MAD in the University Medical Center Groningen (UMCG) for 3 months (February to May 2013). They were 7, 12, 20 and 20 years old at the start of the trial. We offered six patients treatment with MAD, but two decided not to start with the diet. The study was performed according to the legal and ethical guidelines of the UMCG's medical ethics committee.

Modified Atkins diet

Pre-evaluation was made and dietary instructions given according to the recommendations of the international ketogenic diet study group during a 3-day hospital admission.[12] The MAD that was applied included a carbohydrate intake restriction, initially of 0.4 g per kilogram body weight, together with administration of the ketogenic formula: KetoCal 4:1 LQ®/ 12 ml per kilogram body weight. Fat and protein intake were unlimited. The diet was initiated stepwise at home over 7-10 days without fasting. When ketosis was adequately stabilized, carbohydrate intake was increased stepwise by 5 g per day as long as ketosis persisted. Patients were allowed to take extra carbohydrates, on the condition of taking 4 gram extra fat for every gram carbohydrate. Blood ketones and glucose were assessed by twice-daily home monitoring for at least the first month. After the first month stable ketosis had been reached in all patients and blood ketones and glucose measurements were gradually reduced from twice a day to eventually only once a week. On indication patients or their caregivers performed additional sampling of glucose and ketones.

Our dieticians helped the caregivers to offer a wide selection of alternative products to the patients. For instance written dietary exchange lists were provided, and patients were allowed to compensate the carbohydrate intake with fat emulsion, so they could choose their preferred dietary products.

During the first six weeks, the patients visited our multidisciplinary outpatient clinic every 2 weeks. In addition, at least once a week the dieticians had an telephone or e-mail consultation with the patients or their caregivers, or more frequently when necessary (sometimes daily contact).

Data collection

To evaluate the efficacy of the MAD we assessed several clinical parameters at baseline and after 3 months on the diet. HRQL was assessed by using the Dutch Generic Core Scale of the Pediatric Quality of Life Inventory (PedsQL) 4.0.[13] Each patient completed the age-specific version of the PedsQL and, in addition, the parents of the two pediatric patients completed the PedsQL parent proxy report. The PedsQL questionnaire asks patients and their parents to indicate to what extent the patient encountered problems in the last few months before baseline in physical, emotional, social and school-related domains.

From 4 weeks before baseline up until the end of the study, the patients and/or their parents

recorded the seizure frequency in a daily diary. They also recorded any adverse effects of the diet and their perception of the myoclonus severity on a 10-point scale. In addition, an EEG and blinded rating of the myoclonus severity were performed at baseline and after 3 months. For the myoclonus rating we performed a videotaped examination using a standardized protocol. These videos were scored by two independent raters (JG and RZ), blinded for the condition of the patient (baseline or on the diet); they used the Unified Myoclonus Rating Scale (UMRS)[14] and the Clinical Global Impressions Scale.[15]

Furthermore, questionnaires were used to assess mood and behavior. The self-rated version of the Inventory of Depressive Symptomatology (IDS) was used for the two adolescent patients.[16] Mood and behavior in the two youngest patients were measured by a neuropsychologist consultation, with the Child Behavior Check List completed by the parents, the Youth Self Report completed by the patients, and the Caregiver Teacher Report Form, completed by the school teacher. An occupational therapist used the Canadian Occupational Performance Measure (COPM) to identify and prioritize issues that restricted the patient's performance in everyday living; this provided the basis for setting intervention goals.[17] After 3 months, changes in the patient's self-perception of occupational performance were also evaluated with the COPM.

RESULTS

Patient characteristics are shown in Table 1. A detailed description of their clinical phenotypes has been reported elsewhere.[3]

Table 1. Baseline characteristics of the patients

Patient	Sex	Age[a]	Motor function	Seizures	EEG	Medical treatment
1	M	12	Ambulant	Clonic seizures	GED, PCR	CLN, LEV, VPA
2	M	20	Ambulant + wheelchair	Tonic seizures	GED, PCR	CLN, ESM, LEV, VPA
3	M	20	Wheelchair	GTCS	GED, PCR	CLN, ESM, LEV, VPA
4	M	7	Ambulant	No	GED, PCR	None

[a] Age at start modified Atkins diet.
CLN, clonazepam; EEG, electroencephalography; ESM, ethosuximide; GED, frequent generalized epileptic discharges; GTCS, generalized tonic-clonic seizures; LEV, levetiracetam; M, male; PCR, photoconvulsive response; VPA, valproic acid.

All patients completed a 3-month period on the MAD. The diet was well tolerated and none of the patients reported major side-effects. During this period there were no relevant changes in medication or in weight. The patients received 15, 19, 17 and 35 gram of carbohydrates/day respectively, which was also based on bodyweight. Ketosis was reached within 2 weeks in all patients, but significant ketosis was only observed in the youngest patient (patient 4). He became ketotic after just five days on the diet and had average ketones of 4.3 mmol/L (range 2.5 – 6.6 mmol/L). The other child (patient 1) had average ketones of 2.3 mmol/L (range 1.3 – 3.7 mmol/L), while the two young adults had average ketones of 2.2 mmol/L (range 0.8 – 4.4 mmol/L) and 2.6 mmol/L (range 1.3 – 3.5 mmol/L), respectively. Stable ketosis was somewhat easier to achieve in the two youngest patients.

The results of the assessments at baseline and after 3 months on the diet are shown in Table 2. Patient 1 and his mother reported a 40% and 13% improvement in HRQL, respectively. The HRQL scores of patient 3 and 4 also showed improvement (5% and 14% respectively). Patient 2 and the parents of patient 4 reported a deterioration of the HRQL (19% and 39% respectively).

Blinded rating of myoclonus (UMRS), showed small but positive changes in all patient scores (both in rest and in action). The most evident improvements in UMRS score were seen in patients 1 and 2 (aged 12 and 20 years). Seizure frequency remained stable in the three patients who suffered from seizures.

The EEGs of the four patients did not show a relevant decrease of epileptic discharges while on the MAD. Although patient 4 had presented no clinical seizures and only myoclonus and ataxia, his EEG did show epileptic activity and this did not change during the diet period. The results of the complementary assessments of mood, behavior and occupational performance did not show relevant changes in the younger children, but the two adolescent patients reported negative effects. They felt more depressed due to the restricted diet, in particular they missed specific foods such

as bread and potatoes in their daily diet. Their IDS-score declined by 7 and 8 points, respectively. Because the benefits did not match the efforts of maintaining the diet due to its restrictions, patients 2, 3 and 4 discontinued the MAD after a duration of 3, 3 and 5 months, respectively. The provided wide variation of alternative products and menus, and the intensive support from our dieticians could not prevent discontinuation. The parents of the youngest patient (patient 4, aged 7 years) said they would consider to restart the MAD in the future if their child's symptoms would become more severe.

To date, patient 1 is still on the MAD and his HRQL and blinded rating of myoclonus were reassessed after three years on the diet. Compared to the baseline measures, he reported the same HRQL, while his parents reported a sustained improvement of 25%, despite the progressive nature of the disorder. In parallel, the UMRS scores at three years remained broadly unchanged compared to baseline. He showed an improved and sustained physical fitness on the diet, and he recently switched from a school for physically handicapped children to regular secondary education.

Table 2. Results of the assessments at baseline and at 3 months on the Modified Atkins Diet in four patients with North Sea Progressive Myoclonus Epilepsy

Patient	HRQL[a]				UMRS[b]				Effect on seizure frequency[c]	EEG change[c]	Changes in mood and behavior[c]
	Baseline	MAD at 3 months	Change	MAD at 3 years	Baseline	MAD at 3 months	Change	MAD at 3 years			
1	pt. 46 par. 50	pt. 27 par. 43	impr. 19 pts impr. 7 pts	pt 47 par. 37	71	64	impr. 7 pts	75	No change	No changes	n.d.
2	25	31	det. 6 pts	n.a.	72	58	impr. 14 pts	n.a.	No change	No changes	det. IDS 7 pts
3	58	55	impr. 3 pts	n.a.	87	85	impr. 2 pts	n.a.	No change	n.d.	det. IDS 8 pts
4	pt. 28 par. 19	pt. 24 par. 31	impr. 4 pts det. 12 pts	n.a.	57	56	impr. 1 pts	n.a.	n.a	No changes	no relevant change

[a] scores were calculated by the sum of all scores divided by the number of answered items (maximum score 92). A lower score represents a better HRQL
[b] UMRS: scores represent the sum scores of section 2, 3 and items A-G of section 4 of the UMRS, calculated by using the UMRS score sheet.14 A lower score represents less myoclonus; for patient 2, 3 and 4 the scores are the average scores of the two raters; for patient 1 the consensus scores of the two raters are shown in the table (because in the individual scores there was one outlier, so a consensus meeting was organized where the raters rescored all videos together)
[c] change between baseline assessment and 3 months assessment during the MAD
Det., deterioration; EEG, electroencephalography; HRQL, health-related quality of life; IDS, inventory of depressive symptomatology; impr., improvement; MAD, Modified Atkins diet; n.a., not applicable; n.d., no data; par., parents; pt., patient; pts, points; UMRS, Unified Myoclonus Rating Scale

DISCUSSION AND CONCLUSION

Worldwide only 21 NSPME patients have been described.[1-3] In this observational prospective study, we evaluated the efficacy of the MAD in four NSPME patients, with HRQL as our primary outcome measure. In our study one of the four patients showed an improved HRQL on the diet. This 12-year old boy reported a significant (40%) improvement in his HRQL after 3 months on the MAD. He decided to continue on the diet because he felt healthier and less tired, experienced less jerking in the evening and less nocturnal shaking, and could participate more at school and in social events. After 3 years on the MAD, his HRQL has stabilized compared to his baseline, despite the progressive nature of the disease. The other three patients reported varied changes in their HRQL and UMRS while on the diet, but all decided to stop after 3 to 5 months because the benefits were perceived to be too limited compared to their dietary restrictions.

Ketosis in the youngest patient (#4) was excellent while he was on the MAD; compared to the other patients he had milder myoclonus and no clinical seizures, but a comparable HRQL to patient 2, for instance. In this respect it was interesting to observe that his parents thought the burden of the diet was more relevant than the reduction in his myoclonus: they reported a deterioration in the HRQL. However, the patient himself reported a considerable improvement in his HRQL questionnaires, which illustrates that the parents and patient experienced the diet's burden differently, and this influenced their decision to continue the dietary treatment (Table 2).

The levels of plasma ketones of patient 1 were similar to those of patient 2 and 3. The benefit of the MAD observed in patient 1 and lack of benefit in patients 2 and 3 are therefore unlikely to be due to differences in the degree of ketosis achieved during the first three months.

Seizure frequency remained stable in all four patients while on the diet. Although epilepsy was not their main symptom, three of the four patients had generalized tonic, clonic or tonic-clonic seizures with a mean frequency of once a week. Neither the patients nor their parents reported a relevant decrease of seizure frequency while on MAD. EEG findings did not show a change in the epileptic discharges in any of the patients while on the MAD. The UMRS scores showed small, but positive, changes in all the patients on the diet, and the scores of patient 1 at 3 years remained broadly unchanged compared to his baseline, which is remarkable given the progressive nature of the disorder.

Reports on the effect of treatment with the KD in PME are scarce. The KD seems to be particularly effective in generalized forms of epilepsy, including epilepsies with myoclonus.[9, 18] The response rates in the randomized controlled trials of Neal et al. and Lambrechts et al.[6, 7] in children with refractory epilepsy were 38% and 50% respectively, with the percentage of patients who had >50% seizure reduction as the primary outcome measure. In our patients, not epilepsy but myoclonus was the major symptom, reported to interfere most with their activities of daily living. This makes it difficult to compare our results of the controlled KD trials. Despite our study showing improvement in only one out of four patients, for this single case MAD made a major and sustained difference to his HRQL and this was thus an excellent treatment result.

We chose HRQL as the main outcome measure and not seizure frequency or UMRS scores because we considered the sole use of impairment-focused measures to be too limited in scope to evaluate the overall effects of the diet effectively. It has been shown that disease severity rating scales might not always be suited to evaluating the overall effects of an intervention[19], and in small groups of patients it is difficult to detect minor differences on disease severity scales.[20] For these reasons we chose HRQL as our primary endpoint.[19, 20] Koy et al. supported this idea; they described how quality of life can improve significantly in children after deep brain stimulation for dystonia due to cerebral palsy, without any improvement shown on rating scales.[21] Moreover, HRQL likely includes all the different aspects of treatment sequelae in this very rare disorder, and importantly also takes into account the influence of the diet's restrictions on the patient's well-being. This is well illustrated by patient 2, in which an improvement of almost 20% was observed in blinded rating of his myoclonus, but the improvement was counteracted by a deterioration in his mood and a depressed state due to the diet.

There are several limitations to our study. First, we were only able to evaluate four patients and could not include a control group. However, given the rarity of NSPME and the number of patients reported worldwide with this disorder (n = 21), four patients is still a good size group to study. Second, the duration of follow-up of three of the four patients was relatively short because they decided to discontinue the diet.

In conclusion, this observational study shows that one out of four patients with NSPME had a favorable response to the MAD. This patient, who was 12 years old at the start of the study, has been on the diet for more than three years and has a stable HRQL, despite his progressive disorder. Therefore, the MAD might be considered in patients with NSPME, as it may improve or stabilize HRQL in this devastating disorder.

ACKNOWLEDGEMENTS

The authors thank Wieke Eggink and Anouk Kuiper (Department of Neurology, UMCG) for recording the videos; Wencke Veenstra (Department of Neurology, UMCG) for performing the neuropsychological evaluations; Melanie Eissens (Department of Rehabilitation, UMCG) for evaluating the COPM; Esther van Dam (Department of Pediatrics, UMCG) for help with initiation and continuation of the diet, and Jackie Senior (Department of Genetics, UMCG) for critically revising the manuscript.

REFERENCES

1. Corbett MA, Schwake M, Bahlo M, et al. A mutation in the golgi qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. Am J Hum Genet 2011;88:657-663.
2. Boisse Lomax L, Bayly MA, Hjalgrim H, et al. 'North sea' progressive myoclonus epilepsy: phenotype of subjects with GOSR2 mutation. Brain 2013;136:1146-1154.
3. van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by GOSR2 mutation. Mov Disord 2014;29:139-143.
4. Malek N, Stewart W, Greene J. The progressive myoclonic epilepsies. Pract Neurol 2015;15:164-171.
5. Fujimoto A, Yamazoe T, Yokota T, et al. Clinical utility of vagus nerve stimulation for progressive myoclonic epilepsy. Seizure 2012;21:810-812.
6. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500-506.
7. Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand 2017;135:231-239.
8. Freeman JM, Vining EP, Pillas DJ, et al. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics 1998;102:1358-1363.
9. Wheless JW and Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. Epilepsia 2003;44 Suppl 11:27-37.
10. Porta N, Vallee L, Boutry E, et al. Comparison of seizure reduction and serum fatty acid levels after receiving the ketogenic and modified atkins diet. Seizure 2009;18:359-364.
11. Kossoff EH, Dorward JL, Turner Z, et al. Prospective study of the modified atkins diet in combination with a ketogenic liquid supplement during the initial month. J Child Neurol 2011;26:147-151.
12. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia 2009;50:304-317.
13. Varni JW, Burwinkle TM, Seid M, et al. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3:329-341.
14. Frucht SJ, Leurgans SE, Hallett M, et al. The unified myoclonus rating scale. Adv Neurol 2002;89:361-376.
15. Busner J and Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4:28-37.
16. Rush J, Carmody T, Reimitz P. The inventory of depressive symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. International Journal of Methods in Psychiatric Research 2000;9:45-59.
17. Law M, Baptiste S, McColl M, et al. The Canadian occupational performance measure: an outcome measure for occupational therapy. Can J Occup Ther 1990;57:82-87.
18. McTague A and Cross JH. Treatment of epileptic encephalopathies. CNS Drugs 2013;27:175-184.
19. Gimeno H, Tustin K, Selway R, et al. Beyond the Burke-Fahn-Marsden dystonia rating scale: deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol 2012;16:501-508.
20. Eggink H, Kuiper A, Peall KJ, et al. Rare inborn errors of metabolism with movement disorders: a case study to evaluate the impact upon quality of life and adaptive functioning. Orphanet J Rare Dis 2014;9:177,014-0177-6.
21. Koy A, Hellmich M, Pauls KA, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: a meta-analysis. Mov Disord 2013;28:647-654.

CHAPTER 9

Summary and general discussion

SUMMARY

In this thesis, we focused on two treatment modalities for children with epilepsy. Part A comprises pharmacotherapy, the keystone in the treatment of patients with epilepsy. Part B deals with the ketogenic diet, one of the alternative treatment options for children with epileptic seizures resistant to antiepileptic drugs (AEDs).

PHARMACOTHERAPY

The main aims of our studies discussed in the first part of this thesis were to evaluate the evidence for the use of second generation AEDs in children, with a focus on monotherapy; to gain more insight in daily use and prescription patterns of AEDs in children; and to provide scientific substantiation for the increasing use of levetiracetam (LEV) monotherapy in children.

In **Chapter 2**, we reviewed all randomized controlled trials (RCTs) that had been performed with second-generation AEDs used as monotherapy in children before 2010. Second-generation AEDs appeared to be equally effective as first-generation AEDs with respect to both efficacy and safety. The newer drugs were not associated with less side effects, but the nine identified RCTs all had methodological flaws and were, therefore, unable to provide new evidence for decision making.

In **Chapter 3**, we evaluated prescribing patterns of AEDs in Dutch children from 2006-2014. As expected, and in line with national guidelines, the prescribing of new second- and third-generation AEDs increased at the expense of old first-generation AEDs. In 2006 valproic acid (VPA) was still the most frequently initiated AED, in 2010 the number of prescriptions of old and new AEDS were equal, and from 2012 onwards LEV was the most often prescribed AED.

In **Chapter 4**, we presented a systematic review of LEV monotherapy in children with epilepsy. Even though 32 studies on LEV monotherapy in children had been performed, data appeared to be still insufficient to confirm that LEV is effective as initial monotherapy for different seizure types, epilepsy types, and/or epilepsy syndromes. Although efficacy and tolerability seemed good and comparable to other AEDs, the formal evidence for LEV monotherapy in children remained unchanged, mainly due to the designs of the performed studies.[1] They were not all double-blinded, data could not be extrapolated to other seizure and epilepsy types, duration of follow-up was too short, and/or no adequate control AED was used. It only has been proven potentially efficacious for children with focal epilepsy with centrotemporal spikes.

To provide the highest level of evidence for LEV monotherapy in children, we initiated a multicenter RCT in the Netherlands comparing LEV and VPA as monotherapy in children with newly diagnosed epilepsy. Unfortunately, we had to stop the trial prematurely because the recruitment rate was too low. In **Chapter 5**, we critically analyzed the reasons for this, partly based on the responses to a questionnaire we sent out to and which was completed by all investigators. Main reasons

for recruitment failure were overestimation of the number of eligible AED naive children referred by general pediatricians; personal preferences of investigators for specific antiepileptic drugs; and resistance of investigators to include children because of the extensive administrative load due to extra regulations and guidelines for children. Due to logistic, regulatory, legal and ethical restrictions, involving children in RCTs is balancing between protection and participation. Based on our disappointing experience we formulated some general recommendations to increase the feasibility of a similar study. Firstly, to set up intensive collaboration with referring pediatricians. Secondly, to incorporate the possibility of extending the recruitment period. Finally, to arrange support of a clinical trials unit and a local research nurse during the complete trial period. To be able to give this kind of support to independent investigator-initiated trials, adequate fundraising is absolutely necessary.

KETOGENIC DIET FOR PHARMACORESISTANT EPILEPSY

The second part of this thesis contains some studies by which we aimed to increase awareness of the impact of treating children with epilepsy by means of ketogenic diet (KD), especially in emergency situations, and to investigate whether the KD could be applied more easily and might be effective for a unique group of children with pharmacoresistant epilepsy.

All children on KD have a personalized emergency protocol because, especially in emergency situations, an accurate and prompt response is required. In **Chapter 6,** we presented a case to illustrate the importance of such a personalized protocol and to stress the possible consequences if this protocol is not followed strictly.

In **Chapter 7**, we described the results of a prospective, observational study performed in children who started KD as an all-liquid formulation. Despite the low positive response rate to the KD, due to the selection of patients, introduction of KD with a liquid formulation is feasible. Tolerability and acceptance were good, and the diet can be safely introduced in an outpatient setting. The mean time to achieve stable ketosis was less than 7 days, with a median time-to-response of 2 weeks. In our opinion it is possible to evaluate the efficacy of this type of KD within 6 weeks, instead of the current 3.5 months.

In **Chapter 8**, we evaluated the application of the Modified Atkins Diet in a unique group of four young adolescents with pharmacoresistant North Sea Progressive Myoclonus Epilepsy.[2] Health-related quality of life improved considerably in one of them and showed sustained improvement during long-term follow-up, despite the progressive nature of the disorder.

GENERAL DISCUSSION

Trials with antiepileptic drugs in children with epilepsy

The majority of children with epilepsy are treated with AEDs aiming at an optimal balance between suppression of seizures (efficacy) and no or acceptable side effects (tolerability). Attention for possible cognitive and behavioral side-effects is especially crucial in children, since these may negatively affect psychomotor development with consequences for learning, quality of life, and future career prospects.[3] Despite the development and marketing of many new second- and third-generation AEDs, sound scientific evidence for the best possible choice for one or more of these medications in the treatment of children with epilepsy is lacking, mainly due to the limited quality of the design of the studies involved.[1] Prescription of second-generation AEDs has still increased at the expense of first-generation AEDs (Chapter 3), although this implies off-label prescription of various AEDs to children. Levetiracetam monotherapy in children below 16 years is a good example of such off-label use (Chapter 4). The large efforts to develop and register new AEDs are in sharp contrast with the limited available evidence for their use in children. This problem is well recognized by the International League Against Epilepsy. Suggestions to overcome this situation include diminishing regulatory obligations, setting-up collaborative networks, and, last but not least, funding. The Pediatric Regulation came into effect within the European Union in 2007.[4] This regulation aims to improve the health of children in Europe, and requires that all applications for marketing authorization of new medicines include the results of studies performed in children. Furthermore, various networks have been set up, such as the Medicines for Children Research Network (MCRN), the European Network of Paediatric Research (Enpr-EMA), Priority Medicines for Children (PrioMedChild) and StaR Child Health.[5-8] By developing guidelines for clinical trials in children through facilitating collaborations and financially supporting such studies, these networks aim to promote the availability of registered new drugs for children.

Despite all these promising initiatives, we have experienced ourselves that performing clinical trials in children with epilepsy, specially randomized controlled trials (RCTs), is quite difficult (Chapter 5). The pharmaceutical companies are forced to conduct clinical trials to obtain marketing license, and as a consequence these trials comply to fulfill regulatory requirements, including Good Clinical Practice.[9] But are these regulatory studies useful in clinical practice? Do they answer the questions that we, as health providers, have? After all, we do not use placebo in daily practice, we do not treat children who all have the same epilepsy syndrome, we do not use the same titration schedule for every individual child, and we are not only interested in efficacy of the AED. Balancing between the regulatory requirements, including different demands on determining efficacy between the European Medicines Agency (EMA) and Food and Drug Administration (FDA), and questions that need to be answered for clinical practice remains an issue.

Non-regulatory comparative efficacy trials, like the failed LEV-VPA Study (NTR3784), better correspond to clinical practice. However, they obviously also have limitations that have to be taken into account.[9] As stated before, restricted financial resources probably is the most important one to deal with.

The infrastructure of existing networks and the use of electronic health records, containing the same elements and field codes, may promote the performance of registry-based trials. EpiCARE, a European Reference Network for rare and complex epilepsies, is an example of such a network that aims to create significantly added value for patient care, research, education and training in Europe.[10] Performing clinical trials with data received from an electronic health record is not the only solution, and requires, among other things, a very accurate data input.

Recently, the legislation for registration of new AEDs has changed. Data regarding efficacy of an AED for focal seizures in adults may now be extrapolated to children from two years of age.[11]

Hopefully, the initiatives mentioned above will enhance the setting up of high-quality, pragmatic, comparative trials in children with epilepsy. This can only be successful with major investments from both governmental and pharmaceutical research-funding organizations.

Development of new antiepileptic drugs and compounds

The last ten years again new AEDs were approved, such as brivaracetam, eslicarbazepine acetate, lacosamide, perampanel, and retigabine. These third-generation AEDs still have to proof their long-term efficacy and tolerability. Despite all these newer drugs, about 30% of patients with epilepsy are still pharmacoresistant.[12, 13] One might therefore question whether the present methods of identifying new seizure suppressing compounds is the best way to proceed.

One of the recent new advances in epilepsy pharmacotherapy is the use of small molecules. These synthetic chemicals with low molecular weight are widely distributed throughout the body and can cross biological membranes, with the potential to modulate intracellular and extracellular targets.[14] These orally available, stable, inexpensive, permeable drugs have good blood–brain barrier penetration and affinity to brain tissue. Because of their pharmacokinetics, a lower dose is needed, leading to less drug-drug interactions and/or side effects. Selurampanel, for example, is a promising alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor antagonist, that mediates fast excitatory neurotransmission and shows good tolerability and efficacy in the first small clinical trials.[14]

Targeted treatment in children with epilepsy

Targeted therapy is the best medical treatment known for a specific group of children/epilepsy syndromes, based on results of trials or on pharmacological background. Thanks to increased insight into disease pathophysiology and new data provided by trials, targeted treatments are available for certain epilepsy syndromes.[15] Ketogenic diet for children with GLUT-1 deficiency syndrome is a well-known example of targeted therapy, since it bypasses the defective glucose transport across the blood-brain barrier. Another example is stiripentol which is used in children with severe myoclonic epilepsy in infancy (SMEI).[15] The underlying mechanism of its effect in SMEI is still unclear, and the response was discovered by chance when stiripentol was first studied as add-on treatment in children with refractory epilepsy.[16]

Major progress in the field of genetics allowing individual genome analysis at relatively low cost also broadened the field of pharmacogenomics, i.e. the study of the role of the genome in drug response. Pharmacogenomics reflects the combination of pharmacology and genomics, for instance enabling identification of genomic predictors of idiosyncratic side effects of AEDs.[17] The increased risk of carbamazepine induced Stevens-Johnson syndrome in populations with *HLA-B*1502* is a nice example.[18]

Precision medicine in children with epilepsy

Precision medicine refers to the tailoring of medical treatment and to classify individuals into a subpopulation based on their individual characteristics. These subpopulations share the same susceptibility in their response to a specific treatment. These well-defined groups of patients with the same treatable factors can be offered a tailored therapy based on molecular level.[19] An example is everolimus, which inhibits the overactive mTOR pathway in children with tuberous sclerosis.[20]

Despite the discovery of many epilepsy genes thanks to the possibilities of next generation sequencing, understanding the pathophysiological consequences of a gene mutation remains challenging. Precision medicine attempts to modify the effect caused by the mutation, whether it is associated with gain-of-function or loss-of-function. Hypothetically, the potassium channel blocker quinidine would have a positive effect on patients with a KCNT1 (sodium-dependent potassium channel) gain-of-function mutation. One of the case reports indeed stated a decrease of epileptic spasms as well as improvement of development in a patient with West syndrome treated with quinidine.[21] A recent randomized trial did not show, however, any benefit of quinidine in patients with autosomal dominant nocturnal frontal lobe epilepsy due to the same KCNT1 mutation.[22] These two different findings point out the problem that more (genetic) factors may contribute to variability in response to the same drug. To speed up the development of precision medicine, it is vital to collaborate and share data (Figure 1).

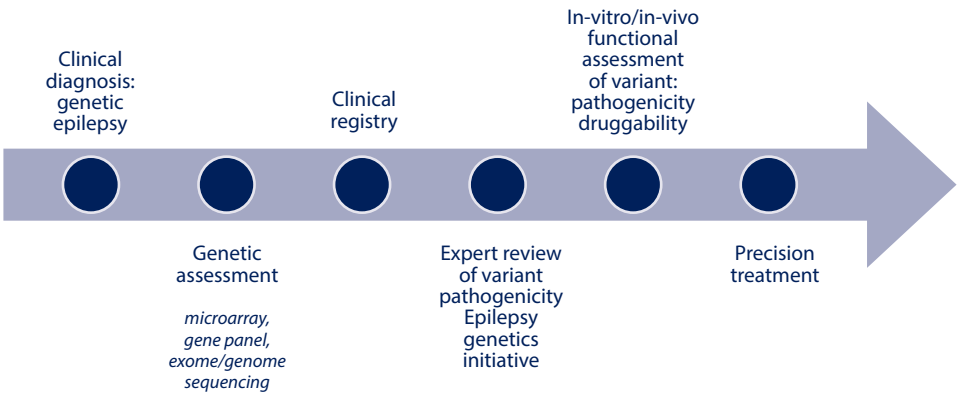

Figure 1. Precision medicine in epilepsy

Adapted with permission from EpiPM consortium, 2015[23]

Apart from these issues in monogenic epilepsies, even more uncertainties arise in polygenic epilepsies. Fortunately, due to the discovery of many genes that are involved in epilepsy, the availability of good animal and in-vitro-models, and the ability to assess efficacy of experimental targeted treatments in small clinical trials, the development of new 'precision medicines' for patients with epilepsy seems realistic and promising.[23] An ideal pre-clinical model of genetic epilepsy translates a genetic mutation into a single phenotype. An integrated approach across different models, like single-cell models, network-scale models, and whole-animal models, provides the best ability to understand the pathological consequences of a mutation.[23] More sophisticated genetic research with approaches including transcriptomes, metabolomes, and the expanded use of whole genome sequencing might improve further understanding of the basic mechanisms underlying epilepsy.[24]

To extend precision medicine into clinical practice, collaboration between clinical, genetic and biological researchers is crucial. Together, they may be capable of investigating large cohorts of individual fully characterized patients, prevalence of mutations in cases and controls, functional consequences of gene mutations, and new AEDs in clinical trials. Hopefully, with all their efforts and collaborations, platforms such as Epilepsy Genetics Initiative[25] and Pediatric Epilepsy Research Consortium[26] are able to further improve the outcome of patients with epilepsy, i.e. treating the underlying disease process instead of suppressing seizures on a more general level.

Future perspectives of other treatment modalities in children with epilepsy

Parallel to the development of new AEDs, major progress has been made with the advancement of other treatment modalities for pharmacoresistant epilepsy.

Medicinal cannabis is one of the most frequently discussed treatment options nowadays and the interest in this product is still growing.[27] The mainly tested component of cannabis is cannabidiol (CBD), whereas 9-delta-tetrahydrocannanidiol (THC) is less interesting because of its psychoactive characteristics. Recently, three RCTs have been performed with CBD regarding efficacy in children with either Dravet syndrome or Lennox-Gastaut syndrome.[28-30] In general, CBD appeared to be superior to placebo with respect to seizure reduction.[31] However, the majority of the patients were also on clobazam treatment. As CBD increases the serum concentration of clobazam and its active metabolite (N-desmethylclobazam) by the inhibitory effect on CYP450 iso-enzymes CYP3A4 and CYP2C19, it is still unclear whether CBD itself or the interaction with clobazam led to this effect. Unfortunately, sub-analyses of the children with and without clobazam were not performed and it is being debated why this was not done.[32] Therefore, the implications of drug-drug interaction should be investigated in more detail to proof whether it is the effect of CBD alone or also the increase of the active metabolite of clobazam.[33]

The role of THC is also still subject of research. CBD/THC has been studied in a prospective open label trial in children with Dravet syndrome and was shown to be safe and well tolerated.[34] Furthermore, secondary objectives showed a reduction in seizure frequency and spike index on EEG, as well as improvement of quality of life.

The efficacy of ketogenic diet (KD) in children with pharmacoresistant epilepsy has been proven, although the anticonvulsant mechanism is still unknown.[35, 36] KD has major consequences in daily life, due to the strictness of the diet. Apart from trying to discover the anticonvulsant mechanism of the diet, another important issue is to explore whether less strict variants of the classical KD may be as effective as the classical KD. Neal et al. have shown that a less restrictive variant with medium-chain triglycerides is effective as well, though this variant is rather strict too.[37] If other more liberal variants prove to be as effective as the classic KD, probably more children will be treated with this diet. Although KD is an option after failure of two AEDs at the moment, because of all baseline investigations that have to be done it is easier for both parents and child, as well as for the doctor, to try a third AED than to follow a very strict diet.

Cyclic fasting, which has less impact on daily life, also leads to increased levels of ketone bodies.[19] Currently, a clinical trial to investigate the effect of KD or cyclic fasting on brain tumors is being performed.[38] Besides people with cancer, children with pharmacoresistant epilepsy could be the population to investigate with respect to the efficacy of cyclic fasting on seizure frequency and well-being. Treatment with KD requires a multidisciplinary team, including a pediatric neurologist, specialized dietician, pediatrician metabolic diseases, and a specialized nurse. It can be hard to have all these specialists in one center, especially in an epilepsy clinic. Cooperation with various centers is necessary to guarantee the safety of the children treated with KD at any moment.

Of the surgical treatment modalities, most progression has been made in epilepsy surgery, especially for adults and children without a lesion on MRI.[39] On the other hand, also children with multiple MRI abnormalities or multifocal EEG abnormalities are sometimes being operated. The resection of the zone that is most epileptogenic may result in improved seizure control, which can have great impact in children with an epileptic encephalopathy.[39] Epilepsy surgery should be performed as early as possible (when indicated), because of a correlation with a higher IQ, less impact of continuing seizures on the structure and function of the brain, and less negative effects of AEDs on cognition.[40-43] In Europe, the presurgical process and outcome in patients from two cohorts including adults and children was compared over time (1997-1998 vs 2012-2013). It was shown that the mean duration of the time period between diagnosis and epilepsy surgery in children had decreased from 5.9 years to 4.8 years.[44] Together with the advancement in surgical methods, more children will be suitable candidates for epilepsy surgery.[44]

Neurostimulation is only indicated for patients with pharmacoresistant epilepsy. It is subdivided in vagus nerve stimulation (VNS), responsive neurostimulation (RNS), and deep brain stimulation (DBS). VNS is the least invasive of the three options and is licensed in both Europe and the United States, also for children. Data regarding efficacy in children is limited and vary, and only one RCT in children has been published.[45, 46] Advances in VNS technology are based on the detection of ictal tachycardia and the newest models are equipped with new software.[47] The RNS® device is implanted in the cranium and provides a closed-loop reaction of electrical stimulation to possible electrocorticographic (ECOG) seizure activity.[48] This device is only approved by the FDA and just for adults. The results of the first trials in adults are promising,[49] and recently three case reports of RNS

in children with positive findings were published.[50, 51] Probably, this is the kickoff for more trials in children with RNS, leading to approval for children in the United States, as well as in Europe. DBS was first approved in Europe and only very recently by the FDA as well.[52] Like VNS, DBS might be effective for patients with generalized or multifocal epilepsy, since DBS delivers electrical stimulation to the thalamus in order to modulate cortical excitability. Of 40 children with pharmacoresistant epilepsy treated with DBS, described in 21 different studies, 12.5% became seizure free and 85% had seizure reduction.[53] However, before DBS can be used more generally in a specific subset of children, more should be known about the optimal target and best settings for DBS, as well as about efficacy and tolerability.

CONCLUSIONS

Epilepsy is the most frequent chronic neurological disorder in children and the majority of children with epilepsy are treated with AEDs. Despite the development and availability of more than 30 AEDs, evidence for their efficacy and tolerability in children with epilepsy is generally limited. Our studies have shown that, despite this limited evidence, the use of newer AEDs in the younger age group is still increasing and off-label prescription has become routine care. More research is therefore needed, but is difficult due to logistic, regulatory, legal and ethical issues. Changes in the legislation for registration of new AEDs, together with instituting collaborating networks will hopefully lead to more evidence based pharmacotherapy. Furthermore, in the near future precision medicine may become the keystone in the treatment of children with epilepsy.

Other treatment modalities will always be needed in those children who are pharmacoresistant and in the future some of them might even become first choice. Better insight in the mechanisms of CBD, ketogenic diet and neurostimulation together with advancements in epilepsy surgery will hopefully lead to broader applicability of all these modalities and a better life for children with epilepsy.

REFERENCES

1. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551-563.
2. van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by GOSR2 mutation. Mov Disord 2014;29:139-143.
3. Moavero R, Santarone ME, Galasso C, et al. Cognitive and behavioral effects of new antiepileptic drugs in pediatric epilepsy. Brain Dev 2017;39:464-469.
4. European Parliament. Paediatric regulation L 378. Offical Journal of the European Union 2006;49:1-21.
5. Medicines for children research network.
   http://mcrn.nl/
6. Ruperto N, Eichler I, Herold R, et al. A european network of paediatric research at the European Medicines Agency (enpr-EMA). Arch Dis Child 2012;97:185-188.
7. Priority Medicines for Children
   www.era-learn.eu/network-information/networks/priomedchild
8. Klassen TP, Hartling L, Hamm M, et al. StaR child health: an initiative for RCTs in children. Lancet 2009;374:1310-1312.
9. Perucca E. From clinical trials of antiepileptic drugs to treatment. Epilepsia Open 2018;3:220-230.
10. EpiCARE.
    https://epi-care.eu/
11. Pellock JM, Arzimanoglou A, D'Cruz O, et al. Extrapolating evidence of antiepileptic drug efficacy in adults to children ≥2 years of age with focal seizures: the case for disease similarity. Epilepsia 2017;58:1686-1696.
12. French JA. Refractory epilepsy: clinical overview. Epilepsia 2007;48 Suppl 1:3-7.
13. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51:1069-1077.
14. Greco M, Varriale G, Coppola G, et al. Investigational small molecules in phase II clinical trials for the treatment of epilepsy. Expert Opin Investig Drugs 2018;27:971-979.
15. Vezyroglou K and Cross JH. Targeted treatment in childhood epilepsy syndromes. Curr Treat Options Neurol 2016;18:29-016-0407-4.
16. Perez J, Chiron C, Musial C, et al. Stiripentol: efficacy and tolerability in children with epilepsy. Epilepsia 1999;40:1618-1626.
17. Franco V and Perucca E. The pharmacogenomics of epilepsy. Expert Rev Neurother 2015;15:1161-1170.
18. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486.
19. Rosenow F, van Alphen N, Becker A, et al. Personalized translational epilepsy research - novel approaches and future perspectives: Part I: clinical and network analysis approaches. Epilepsy Behav 2017;76:13-18.
20. French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet 2016;388:2153-2163.
21. Fukuoka M, Kuki I, Kawawaki H, et al. Quinidine therapy for west syndrome with KCNTI mutation: a case report. Brain Dev 2017;39:80-83.
22. Mullen SA, Carney PW, Roten A, et al. Precision therapy for epilepsy due to KCNT1 mutations: a randomized trial of oral quinidine. Neurology 2018;90:e67-e72.
23. EpiPM Consortium. A roadmap for precision medicine in the epilepsies. Lancet Neurol 2015;14:1219-1228.

24. Myers KA, Johnstone DL, Dyment DA. Epilepsy genetics: current knowledge, applications, and future directions. Clin Genet 2019;95:95-111.
25. Epilepsy genetics initiative. https://www.cureepilepsy.org/egi/
26. Pediatric epilepsy research consortium. https://pediatricerc.com/
27. Perucca E. Cannabinoids in the treatment of epilepsy: hard evidence at last? J Epilepsy Res 2017;7:61-76.
28. Devinsky O, Cross JH, Wright S. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;377:699-700.
29. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378:1888-1897.
30. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with lennox-gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:1085-1096.
31. Elliott J, DeJean D, Clifford T, et al. Cannabis-based products for pediatric epilepsy: a systematic review. Epilepsia 2019;60:6-19.
32. Groeneveld GJ and Martin JH. Parasitic pharmacology: A plausible mechanism of action for cannabidiol. Br J Clin Pharmacol 2019; DOI: 10.1111/bcp.14028
33. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia 2015;56:1246-1251.
34. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in Dravet syndrome. Ann Clin Transl Neurol 2018;5:1077-1088.
35. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500-506.
36. Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand 2017;135:231-239.
37. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia 2009;50:1109-1117.
38. Rieger J, Bahr O, Maurer GD, et al. ERGO: a pilot study of ketogenic diet in recurrent glioblastoma. Int J Oncol 2014;44:1843-1852.
39. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol 2014;13:1114-1126.
40. Freitag H and Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 2005;46:561-567.
41. Van Schooneveld MM and Braun KP. Cognitive outcome after epilepsy surgery in children. Brain Dev 2013;35:721-729.
42. Braun KP. Preventing cognitive impairment in children with epilepsy. Curr Opin Neurol 2017;30:140-147.
43. Braun KPJ and Cross JH. Pediatric epilepsy surgery: the earlier the better. Expert Rev Neurother 2018;18:261-263.
44. Baud MO, Perneger T, Racz A, et al. European trends in epilepsy surgery. Neurology 2018;91:e96-e106.
45. Morris GL,3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the guideline development subcommittee of the American Academy of Neurology. Epilepsy Curr 2013;13:297-303.
46. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Dev Med Child Neurol 2012;54:855-861.
47. Wheless JW, Gienapp AJ, Ryvlin P. Vagus nerve stimulation (VNS) therapy update. Epilepsy Behav 2018;88S:2-10.

48. Benbadis SR, Geller E, Ryvlin P, et al. Putting it all together: Options for intractable epilepsy: an updated algorithm on the use of epilepsy surgery and neurostimulation. Epilepsy Behav 2018;88S:33-38
49. Geller EB. Responsive neurostimulation: review of clinical trials and insights into focal epilepsy. Epilepsy Behav 2018;88S:11-20.
50. Kokoszka MA, Panov F, La Vega-Talbott M, et al. Treatment of medically refractory seizures with responsive neurostimulation: 2 pediatric cases. J Neurosurg Pediatr 2018;21:421-427.
51. Singhal NS, Numis AL, Lee MB, et al. Responsive neurostimulation for treatment of pediatric drug-resistant epilepsy. Epilepsy Behav Case Rep 2018;10:21-24.
52. Salanova V. Deep brain stimulation for epilepsy. Epilepsy Behav 2018;88S:21-24.
53. Yan H, Toyota E, Anderson M, et al. A systematic review of deep brain stimulation for the treatment of drug-resistant epilepsy in childhood. J Neurosurg Pediatr 2018:1-11.

Nederlandse samenvatting

Epilepsie is een hersenaandoening waarbij epileptische aanvallen kunnen ontstaan door een disbalans in signaaloverdracht in de hersenen. De klinische verschijnselen van een epileptische aanval zijn heel divers en zijn afhankelijk van het gebied en de intensiteit van de abnormale hersenactiviteit. De diagnose epilepsie kan worden gesteld als iemand minstens twee epileptische aanvallen heeft gehad met een interval van meer dan 24 uur en die aanvallen zijn niet door bepaalde omstandigheden (bijv. slaaptekort of koorts) uitgelokt. Dat kan ook bij één dergelijke niet uitgelokte aanval als de kans op herhaling daarvan wordt geschat op tenminste 60% binnen tien jaar, of als op basis van één of meer aanvallen een epilepsie syndroom kan worden vastgesteld. Een epilepsiesyndroom omvat een vaste combinatie van epileptische aanvallen, beginleeftijd en EEG afwijkingen (bijv. absence epilepsie).

Op de kinderleeftijd komt epilepsie veel voor. Dat komt omdat er onder de (aangeboren) aandoeningen die zich openbaren op de kinderleeftijd veel zijn waar epilepsie bij voorkomt, zoals stofwisselingsziekten of aanlegstoornissen van de hersenen. Bovendien zijn hersenen van kinderen nog volop in ontwikkeling en kan gemakkelijker een verstoring van signalen in de hersenen optreden.

Indien de diagnose epilepsie is gesteld, is de volgende stap de oorzaak ervan te achterhalen, omdat dit behandelconsequenties kan hebben en mogelijkerwijs iets over het verloop kan voorspellen. Voor veel kinderen met epilepsie is er reden voor behandeling met anti-epileptica, medicijnen waarmee we proberen de epileptische aanvallen te onderdrukken.

Sinds de vorige eeuw zijn veel anti-epileptica ontwikkeld en spreken we inmiddels van eerste generatie (op de markt gekomen vóór 1990), tweede generatie (1990-2005) en derde generatie anti-epileptica (na 2005). Ondanks dat deze medicijnen de hoeksteen vormen van de behandeling van patiënten met epilepsie bestaat er weinig wetenschappelijk bewijs voor de effectiviteit van deze anti-epileptica bij kinderen, zelfs niet van de nieuwere tweede en derde generatie anti-epileptica.

In het eerste deel van dit proefschrift richten wij ons op de behandeling van kinderen met anti-epileptica, met name op de toepassing van tweede generatie middelen, en dan vooral als er maar één anti-epilepticum tegelijk wordt gebruikt (monotherapie). De vraag is hoeveel wetenschappelijke onderbouwing er bestaat voor het bestaande voorschrijfgedrag? Speciale aandacht gaat daarbij uit naar levetiracetam, een tweede generatie anti-epilepticum, waarvan het gebruik bij kinderen en volwassenen de laatste 10 jaar duidelijk lijkt toegenomen.

In **hoofdstuk 2** hebben we alle beschikbare gerandomiseerde gecontroleerde studies (RCTs) tot 2010 geëvalueerd waarin tweede generatie anti-epileptica als monotherapie bij kinderen zijn onderzocht. Afgezien van het feit dat de negen geïdentificeerde onderzoeken allemaal tekortkomingen hadden in de toegepaste methoden en geen nieuw wetenschappelijk bewijs leverden, leken tweede generatie anti-epileptica even effectief als eerste generatie anti-epileptica, zonder belangrijke verschillen in frequentie en ernst van opgetreden bijwerkingen.

In **hoofdstuk 3** hebben we het voorschrijven van anti-epileptica aan Nederlandse kinderen tussen 2006-2014 geëvalueerd. Zoals verwacht zijn de nieuwere tweede en derde generatie anti-epileptica over de jaren steeds vaker voorgeschreven ten koste van de eerste generatie anti-epileptica. Dit is in overeenstemming met nationale richtlijnen. In 2006 was valproïnezuur (eerste generatie) nog steeds het meest als eerste voorgeschreven anti-epilepticum. In 2010 werden eerste en tweede generatie anti-epileptica even vaak gestart, maar vanaf 2012 bleek levetiracetam (tweede generatie) het meest voorgeschreven anti-epilepticum. In **hoofdstuk 4** geven we een systematisch overzicht van de studies met levetiracetam als monotherapie bij kinderen met epilepsie. In de beschikbare 32 studies werd aangetoond dat de effectiviteit en bijwerkingen van levetiracetam goed en vergelijkbaar zijn met die van andere anti-epileptica. Desondanks is als gevolg van de beperkte kwaliteit en toegepaste methoden van deze studies onvoldoende bewijs geleverd voor de toepassing van levetiracetam als initiële monotherapie voor verschillende soorten aanvallen, epilepsietypes en/of epilepsiesyndromen. Het is alleen potentieel effectief gebleken voor kinderen met een bepaalde veelvoorkomende vorm van kinderepilepsie.

Met het doel het toegenomen gebruik van levetiracetam als monotherapie bij kinderen wetenschappelijk te onderbouwen, hebben we een grote RCT opgezet in Nederland. Doel was levetiracetam en valproïnezuur met elkaar te vergelijken als eerste behandeling van kinderen bij wie de diagnose epilepsie is gesteld. Helaas waren we genoodzaakt deze studie voortijdig af te breken, omdat de inclusie van de kinderen structureel veel te laag bleef (15 kinderen in 1,5 jaar t.o.v. 200 benodigde kinderen in 2 jaar). **Hoofdstuk 5** bevat een kritische analyse van de oorzaken van het mislukken van deze studie. Daarbij hebben we gebruik gemaakt van een enquête die op ons verzoek was ingevuld door alle deelnemende onderzoekers. De voornaamste reden van de achterblijvende inclusie was het erg tegenvallende aantal kinderen dat door kinderartsen uit algemene ziekenhuizen werd verwezen voor dit onderzoek. Daarnaast hadden de onderzoekers zelf soms moeite met de randomisatie door een persoonlijke voorkeur voor een bepaald (ander) anti-epilepticum. Ook bestond er een zekere weerstand om kinderen te includeren vanwege de vele administratieve verplichtingen. Deze zijn bij studies met kinderen nog veel uitgebreider dan bij die met volwassenen. Door logistieke problemen, wettelijke regelgeving en ethische dilemma's is het erg moeilijk om dergelijk gerandomiseerd onderzoek bij kinderen uit te voeren en blijft het zoeken naar de juiste balans tussen deelname aan onderzoeken (ook in het belang van de kinderen zelf) en bescherming van het kind op meer individuele basis. We hebben onze ervaringen ook in een bredere context geplaatst en vergeleken met die van andere gerandomiseerde gecontroleerde onderzoeken bij kinderen. Op grond daarvan hebben we een drietal aanbevelingen gedaan om een dergelijke studie succesvol af te ronden: intensiever samenwerken met verwijzende kinderartsen om voldoende kinderen te kunnen includeren, insteken op een lange periode van inclusie en zorgen voor beschikbaarheid van een onderzoeksverpleegkundige in alle deelnemende centra om gedurende het hele onderzoek ondersteuning te kunnen bieden. Dergelijke ondersteuning vraagt om voldoende financiële middelen hetgeen bij onafhankelijke, niet-gesponsorde studies niet eenvoudig is en vergt een grote inspanning van onderzoekers, maar dat zijn we wel aan deze kinderen verplicht. Het effect van medicatie op kinderen en de reactie van kinderen op medicatie is immers bewezen anders. Aanpassingen van de wetgeving rondom registratie van nieuwe

anti-epileptica, het opzetten van netwerken om tot betere samenwerking te komen ook op het gebied van onderzoek, en tot slot het meer bewust worden van het feit dat kinderen geen kleine volwassenen zijn, zullen hopelijk leiden tot betere wetenschappelijke onderbouwing van de medicamenteuze behandeling van kinderen met epilepsie.

Ondanks een groot aantal beschikbare anti-epileptica bereiken we bij ongeveer 1/3 van alle patiënten onvoldoende aanvalscontrole; er is dan sprake van therapieresistente epilepsie. In zo'n geval wordt ook gezocht naar mogelijke niet-medicamenteuze behandelingen. In het tweede deel van dit proefschrift wordt aan één daarvan aandacht besteed, namelijk het ketogeen dieet. Het belangrijkste kenmerk van dit dieet is het grote aandeel vet met een zeer beperkte hoeveelheid koolhydraten. Door het aanbieden van vetrijke voedingsmiddelen en preparaten wordt voornamelijk vet verbrand waardoor ketonlichamen worden gevormd en deze ketonlichamen vormen een alternatieve energiebron voor de hersenen in plaats van glucose. Het exacte werkingsmechanisme is onbekend. Grote gerandomiseerde gecontroleerde studies hebben aangetoond dat het ketogeen dieet bij ongeveer 40% van de kinderen effectief is. Het dieet moet wel zeer strikt worden gevolgd en brengt grote veranderingen in de stofwisseling teweeg. Derhalve heeft ieder kind een persoonlijk noodprotocol waarin opgenomen is hoe te handelen in geval van acute situaties waarbij zorgvuldige en snelle actie is vereist. **Hoofdstuk 6** bevat een klinische les over de toepassing en het belang van een dergelijk individueel noodprotocol. Hierin wordt ook beschreven wat de mogelijke gevolgen zijn als dit protocol niet strikt wordt opgevolgd.

Toepassing van het ketogeen dieet bij een kind heeft een grote impact op het dagelijks leven van zowel kind als ouders/verzorgers. Gemiddeld duurt het 13 weken voordat het effect van het ketogeen dieet formeel wordt beoordeeld en de beslissing wordt genomen het dieet al dan niet te continueren. We hebben daarom een prospectieve, observationele pilotstudie opgezet met als doel deze beslissing mogelijk eerder te kunnen nemen en te evalueren of de praktische uitvoering van het ketogeen dieet ook eenvoudiger kan (**hoofdstuk 7**). Het ketogeen dieet werd thuis geïntroduceerd met hulp van een volledig vloeibaar product (drinkvoeding of sondevoeding) waardoor de uitvoering veel makkelijker was en er veel minder kans op fouten bestond. De beperkte effectiviteit van het ketogeen dieet kwam hoogstwaarschijnlijk door de selectie van deelnemende kinderen met zeer ernstige vormen van epilepsie. Die reageren altijd minder goed dan kinderen met niet-ernstige vormen van epilepsie. Desondanks was het mogelijk het dieet bij de kinderen thuis te starten met een volledig vloeibaar product. De gemiddelde tijd die nodig was om stabiele ketose te bereiken was minder dan 7 dagen en de mediane tijd tot het bereiken van een afname van het aantal aanvallen met minstens de helft was 2 weken. Naar onze mening rechtvaardigt dit het evalueren van de werkzaamheid van deze uitvoering van het ketogeen dieet binnen 6 weken.

Tot slot beschrijven we in **hoofdstuk 8** een studie naar het effect van het gemodificeerde Atkins-dieet, een iets liberalere variant van het ketogeen dieet, bij een unieke groep van vier jonge adolescenten met therapieresistente Noordzeeziekte. Deze langzaam progressieve ziekte begint op jonge leeftijd en wordt gekenmerkt door spierschokken, ongecoördineerd bewegen en epilepsie. De belangrijkste uitkomstmaat in deze studie, de gezondheid-gerelateerde kwaliteit van leven,

verbeterde bij één van de vier patiënten, ondanks het progressieve karakter van de aandoening. Hoewel onze studie kort was en bij slechts vier patiënten werd uitgevoerd, kan naar onze mening dit dieet worden overwogen bij patiënten met deze ernstige invaliderende aandoening.

Het proefschrift eindigt met een algemene discussie (**hoofdstuk 9**) over het gebruik van anti-epileptica bij kinderen en de noodzaak tot het doen van meer onderzoek bij deze leeftijdsgroep. Kijkend naar de toekomst zullen meer anti-epileptica en waarschijnlijk ook medicijnen met een heel ander werkingsmechanisme worden ontwikkeld en op de markt worden gebracht met als doel een steeds meer op het individu gerichte behandeling te kunnen bieden. Naar verwachting zal *precision medicine* hierin een steeds grotere rol in spelen. Daarbij streeft men naar een op het individu gerichte behandeling op basis van eigen kenmerken.

Daarnaast verwachten we ook meer ontwikkelingen op het gebied van andere behandelmogelijkheden, waarvan op korte termijn het gebruik van cannabis-olie (CBD/THC) verder geëxploreerd zal worden. Verfijning van technische mogelijkheden zal ten goede komen aan ontwikkelingen op het gebied van epilepsiechirurgie en neuromodulatie. Dit laatste omvat enkele methoden waarbij een deel van de hersenen elektrisch wordt gestimuleerd om de functie ervan te beïnvloeden. Voorbeelden zijn nervus vagus stimulatie, diepe hersenstimulatie en responsieve stimulatie. Van het ketogeen dieet zal worden onderzocht welke minder strenge varianten dezelfde werkzaamheid hebben als het klassieke ketogeen dieet, maar gepaard gaan met grotere therapietrouw.

Concluderend beschrijven we in dit proefschrift de rol van anti-epileptica bij kinderen met epilepsie en het beperkte beschikbare wetenschappelijk bewijs van de effectiviteit en verdraagbaarheid ervan. Ook hebben we gekeken hoe artsen anti-epileptica aan kinderen voorschrijven, waarbij dus andere factoren dan wetenschappelijk bewijs een rol spelen. We laten zien hoe moeilijk het is goed onderzoek te doen naar effectiviteit en bijwerkingen van anti-epileptica bij kinderen en dat dit een van de redenen is waarom er slechts beperkte beschikbare wetenschappelijke onderbouwing is voor het gebruik ervan door kinderen. Aan de hand van eigen ervaringen doen we suggesties hoe dergelijk onderzoek opgezet zou kunnen worden. Tot slot gaan we in op één van de niet-medicamenteuze behandelmogelijkheden, het ketogeen dieet. We benadrukken het belang van een individueel noodprotocol en van het blijven zoeken naar mogelijkheden om het kinderen en ouders gemakkelijker te maken dit dieet te volgen.

List of publications

A. Weijenberg, J.H.J. Bos, C.C.M. Schuiling-Veninga, O.F. Brouwer, P.M.C.Callenbach. Antiepileptic drug prescription in Dutch children from 2006–2014 using pharmacy-dispensing data. Epilepsy Res 2018;146:21-27

A. Weijenberg, M van Rijn, P.M.C. Callenbach, T.J. de Koning, O.F. Brouwer. Ketogenic Diet in Refractory Childhood Epilepsy: Starting With a Liquid Formulation in an Outpatient Setting. Child Neurol Open. 2018;5:1-7

A. Weijenberg, M. E. van Egmond, M.E. van Rijn, J.W.J. Elting, J.M. Gelauff, R. Zutt, D.A. Sival, R.A. Lambrechts, M. A. J. Tijssen, O.F. Brouwer, T.J. de Koning. The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study. Orphanet J Rare Dis. 2017;12:45

A. Weijenberg, M.E. van Rijn, O.F. Brouwer, T.J. de Koning. Het ketogeen dieet; hoe te handelen in acute situaties. Praktische Pediatrie. 2017, september.

A. Weijenberg, P.M.C. Callenbach, O.F. Brouwer. Investigator-initiated randomized controlled trials in children with epilepsy: mission impossible? Epilepsia Open 2017;2:32-38

A. Weijenberg, O.F. Brouwer, P.M.C. Callenbach. Levetiracetam monotherapy in children with epilepsy: a systematic review. CNS Drugs 2015;29:371-382

A. Weijenberg, J.M.C. van Dijk, J. Pruim, G.J. Luijckx. Teaching NeuroImages: FDG-PET imaging in primary diffuse leptomeningeal gliomatosis. Neurology 2013;81:e119-e120

A. Weijenberg, M. Offringa, O.F. Brouwer, P.M.C. Callenbach. RCTs with new antiepileptic drugs in children: a systematic review of monotherapy studies and their methodology. Epilepsy Res 2010;91:1-9

A. Weijenberg, O.F. Brouwer, E.W. Hoving. Syringomyelie en een chiari-malformatie bij een kind met scoliose. Ned Tijdschr Geneeskd 2008;152:1339-1343.

Dankwoord

Aan de vooravond van mijn eerste zwangerschapsverlof ging ik het commitment aan: ik zou starten met promotieonderzoek. Het was geen standaard traject en het ging ook gepaard met ups-and-downs. Zoals ik altijd heb aangegeven wilde ik alleen promotie onderzoek doen over een onderwerp dat me na aan het hart ligt en met fijne begeleiding en mensen om me heen. En de verwezenlijking van die voorwaarden hebben gemaakt dat het nu af is!

Prof. dr. O.F. Brouwer, mijn promotor en opleider kinderneurologie. Beste Oebo, ik kan me nog goed mijn eerste colleges van jou herinneren. Er volgde een keuze-coschap, een klein wetenschappelijk onderzoekje, een klinische les en uiteindelijk berichtte jij mij dat ik met de opleiding in Groningen mocht beginnen. Dit was de start van jarenlange opleiding en samenwerking. Wat kijk ik daar met plezier en trots op terug. Jouw rustige uitstraling, altijd openstaande deur, vele stapels, maar wel geordend, papier, en begrip maakten dat ik me altijd heel welkom voelde, ook al realiseerde ik me goed dat er aan het einde van de dag weer manuscripten in jouw tas mee naar huis moesten. Toen de inhoud van mijn proefschrift door omstandigheden moest veranderen, kwam jij direct met een alternatief, waardoor ik altijd hoop heb gehouden op een goede afloop. Dank voor het vertrouwen dat je me hebt gegeven; het is ongelofelijk hoe goed jij kan inschatten wanneer er een beetje druk nodig is, of juist even niet.
Ook heb ik erg veel van je geleerd in je hoedanigheid als opleider kinderneurologie. We delen dezelfde passie voor (de behandeling van) epilepsie en kunnen berusten in het feit dat sommige kinderen niet beter worden, maar dat een goede begeleiding dan niet minder waardevol is. De gesprekken die je met ouders voert, maken op velen zeer veel indruk, zo ook op mij en ik pluk daar dagelijks de vruchten van.
Het is bijzonder dat in deze maand ik mijn proefschrift verdedig en jij met emeritaat gaat. Ik wens je toe dat het leven nog veel moois voor jou en je dierbaren in petto heeft. Jouw meest dierbare wil ik ook bedanken. Lieve Nienke, wat is het geweldig leuk dat ook jij zo betrokken bent met arts-assistenten en collega's met wie Oebo werkt. Jouw oprechte interesse en aandacht, samen met een uitstekende verzorging, maakten dat het nuttige vaak verenigd werd met het aangename. Heb het goed samen!

Dr. P.M.C. Callenbach, mijn co-promotor. Beste Petra, onze (indirecte) samenwerking begon toen ik op jouw werkplek mocht zitten en een start maakte met mijn eerste onderzoekje, omdat jij met zwangerschapsverlof was. Dat dit later feitelijk de start bleek van mijn promotieonderzoek had niemand kunnen vermoeden. Jouw gedrevenheid, punctualiteit, betrokkenheid, ervaring en optimisme maakten dat onze samenwerking voortreffelijk liep en dat ik veel van je heb geleerd; heel veel dank daarvoor. Ik had me geen betere copromotor kunnen wensen. Als ik aan deze tijd terug denk, denk ik ook aan alle keren dat jij of ik met zwangerschapsverlof was. Zeven prachtige en gezonde kinderen; dat relativeert alles!

Prof. dr.H.P.H. Kremer, mijn opleider neurologie en lid van de leescommissie. Beste Berry, veel dank voor het kritisch lezen van dit proefschrift , maar bovenal voor het feit dat u mijn opleider was. Kapstokken en rijtjes scheppen structuur, hetgeen voor de opleiding zeer behulpzaam kan zijn. Dat u zelf ook uw hoofd op het hakblok durfde te leggen, maakte dat de sfeer binnen de

opleidingsgroep goed en veilig was.
Beste prof. dr. K.P.J. Braun en prof. dr. H.J.M. Majoie, bedankt voor het lezen en beoordelen van het proefschrift. Dat we (indirecte) collega's zijn, maakt het extra bijzonder dat jullie zitting hebben in de corona.

Leden van het eerste keto-team UMCG: prof. dr. G.P.A. Smit, prof.dr. D.J. Reijngoud, prof. dr. O.F. Brouwer, Greet van Rijn en Bertha Smallenbroek en iets later ook prof. dr. T.J. de Koning. Terugkijkend was het bijzonder dat ik als jongst gediende een behandelprotocol en onderzoeksprotocol schreef voor een behandeling die ik zelf nog nooit had gedaan. Maar met jullie expertise, ervaring en vertrouwen is het wel gelukt en werd ook de eerste keto-poli een feit. Een traject waarvan ik in vele opzichten veel geleerd heb. Wat ontzettend fijn dat er inmiddels opnieuw vorm gegeven is aan het team en dat de patiënten behandeld kunnen blijven worden. Greet, een extra woord van dank aan jou vanwege onze fantastische samenwerking. Een heel verschillende achtergrond, andere generatie en het dan zo goed hebben samen. Ik kijk er met heel veel genoegen op terug. Dank je wel voor alles wat je mij geleerd hebt.

Gedurende de periode dat ik onderzoek deed, wisselde ik vaak van plek. Ondanks dat ik niet tot een onderzoeksgroep behoorde, was de sfeer op de verschillende kamers op de 4e altijd goed en gedreven. Het langst zat ik bij Suzanne en Ellen. Hoewel onze werkzaamheden verschilden, waren de gesprekken over niet werk-gerelateerde zaken erg gezellig en boden jullie vaak een luisterend oor. Dank daarvoor!
Martje, het was leerzaam samen een onderzoek te doen en hiermee onze verschillende aandachtsgebieden samen te brengen. Dank je wel voor de prettige samenwerking.
Oud collega's neurologie van het UMCG. Het is al weer een aantal jaren geleden dat we intensief met elkaar samen werkten, maar het was wel een hele belangrijke periode in mijn leven. Tijdens de borrel ter gelegenheid van het afronden van mijn opleiding tot neuroloog vertelde ik in mijn speech dat ik met 77 AIOS neurologie in het UMCG heb samen gewerkt. Naast hard werken, altijd in goede harmonie en sfeer, waren er sociale activiteiten en vele life events. Dat je dat met elkaar deelt en samen beleeft, maakt dat ik voor altijd een band heb met jullie, ook al zijn we inmiddels verspreid over het hele land en zijn onze agenda's altijd vol. Veel dank aan een ieder met wie ik in die periode zo fijn gewerkt heb, in het UMCG en daarbuiten. Zullen we toch eens streven naar een reünie in 2021?

Kinderartsen Isala Zwolle, hartelijk dank dat ik mijn laatste opleidingsjaar bij jullie kon volgen. Jullie hebben opleiding hoog in het vaandel staan, daar mogen jullie trots op zijn. Veel dank voor de ruimte die ik kreeg, om naast de algemene kindergeneeskunde, ook de kinderneurologie in een groot algemeen ziekenhuis uit te oefenen. Na voornamelijk academische ervaring heb ik daar erg veel van geleerd.

Huidige collega's van SEIN Zwolle, het is een eer te werken met jullie in een centrum waar zoveel expertise is en waar je zo veel voor een patiënt en familie kan betekenen. Het is mooi te ervaren dat we een diverse groep vormen, maar gezamenlijk altijd het beste voor de patiënt nastreven.

Mijn directe collega's kinderneurologen, een team van 4 vrouwen. Samen zijn we in staat het allerbeste voor kinderen met epilepsie te bieden en dat maakt dat ik heel graag met jullie werk!

Lieve vrienden, vriendinnen, jaarclubgenootjes en dispuutsgenootjes. De basis voor de meeste vriendschappen werd gelegd in Groningen en dat betekent dat ik jullie inmiddels al meer dan de helft van mijn leven ken. Allemaal uitgevlogen, maar nog altijd goed contact en fijne momenten met elkaar, wat het leven zo ontzettend aangenaam maakt. Dank daarvoor.
Lieve Klaas&Meike, Okke&Hiltje, Lieuwe&Dianne: ik koester onze vriendschap. Dank jullie wel voor alle liefde en steun.
En toen verhuisden we van Groningen naar Hattem, dat vond ik even wennen. Dank lieve Marc&Hilke voor de eerste kennismaking met Hattem en jarenlange vriendschap. Inmiddels ervaar ik het als een voorrecht in zo'n mooi stadje te wonen en voel ik me rijk met zoveel nieuwe vrienden om me heen. Lieve Anna&Jeroen, de samenstelling van onze gezinnen maakte de klik, maar inmiddels is er zo veel meer dan dat. Dank jullie wel!

Mijn paranimfen, Bregje en Ellen.
Lieve Breg, het is zo fijn om een vriendin te hebben die goed kan luisteren, analyseert, nooit oordeelt, altijd klaar staat en kan genieten van het leven. Wat een geluk dat wij elkaar leerden kennen in ons eerste jaar Groningen, jaarclubgenootjes werden, en sindsdien samen zoveel mooie en leuke momenten hebben beleefd. Ook voor de kinderen ben je een fantastische 'suikertante'. Dank dat je ook vandaag een belangrijke rol in mijn leven speelt.
Lieve Ellen, mijn Soephuis-genootje, mijn dispuutgenootje, maar bovenal lieve vriendin. Wie had ooit kunnen vermoeden dat we 20 jaar later 200 meter van elkaar in Hattem zouden wonen? We hebben al zoveel samen gedeeld, zoals een wc-schrift, tutorgroep, ontgroening, de eerste ervaring als arts-assistent, weekendjes weg, doen van wetenschappelijk onderzoek, vele borrels en feesten met als hoogtepunt ons huwelijksfeest. Dank je wel voor je trouwe aandacht, luisterend oor en uitgestoken hand. Heel veel succes met de laatste loodjes van jouw proefschrift; ik heb er alle vertrouwen in dat dat goed komt en ik hoop dat onze gezinnen altijd nauw met elkaar verbonden zullen blijven.

Lieve Karel en Mia, ik hoop op eenzelfde manier jullie leeftijd te bereiken. Ongelofelijk hoe actief jullie zijn en wat jullie van het leven maken. Genietend in al z'n eenvoud met liefde voor de natuur, muziek en medemens, maken jullie hele fijne schoonouders.

Lieve Anke, mijn lieve, zorgzame, wijze en bescheiden schoonmoeder. Heel veel dank voor al je aandacht, interesse en hulp. Ik zie je stilzwijgend intens genieten van onze kinderen en hoop dat zij zich realiseren hoezeer ze boffen met jou als oma. Hopelijk gaat de vakantie volgend jaar wel door.

Willemijn en Libertien, mijn lieve zussen! Alledrie hebben we een eigen richting gekozen qua opleiding, werk en woonplaats, maar het blijft zo fijn om met jullie samen te zijn. Kwaliteit gaat absoluut boven kwantiteit. Nu we allemaal getrouwd zijn en een gezin hebben, is de band nog intenser geworden. Jullie kinderen voelen ook een beetje als mijn kinderen en het is geweldig

samen met jullie op vakantie te gaan en samen te genieten van alle mooie dingen in het leven. Dank jullie wel voor jullie liefde, hulp en betrokkenheid. Ik ben er trots op dat jullie mijn zussen zijn! 2e weekend van maart?!

Lieve mamma en pappa. De basis voor alles wat ik in het leven heb kunnen doen, is door jullie gelegd. Optimisme, zelfstandigheid, betrokkenheid, vertrouwen, onvoorwaardelijke steun en liefde vormen hierin de sleutel. Ik weet dat jullie trots zijn op mij, maar wees dat vandaag ook op jullie zelf. Geen autoritje is jou teveel pappa, en geen actie is jou teveel mamma. Sinds de komst van onze kinderen zijn jullie opnieuw verliefd en ik besef erg goed hoe bijzonder de band tussen onze kinderen en jullie is. Nu er een nieuwe periode in jullie leven is aangebroken, hoop ik dat jullie in goede gezondheid volop kunnen blijven genieten van elkaar en het leven, en dat wij daar van heel dicht bij altijd deel van uit blijven maken. Ik hou van jullie.

Lieve Stije, Lidewij en Deirdre, jullie zijn het grootste cadeau in mijn leven. Jullie geven mij zoveel energie, liefde en geluk en helpen mij goed te kunnen relativeren. Ik geniet intens van jullie onbevangenheid. Dit boekje is voor jullie nog abstract, maar jullie weten wel dat ik ergens druk mee bezig was. Wellicht begrijpen jullie later waarmee dat precies was. Hopelijk zal opa's uitspraak 'concentratie is prestatie' ook jullie helpen dat te bereiken in het leven waar je gelukkig van zal worden.

De laatste woorden van dit dankwoord zijn voor mijn grote liefde. Lieve Hans, al ruim 18 jaar ben jij de allerbelangrijkste persoon in mijn leven. Heel veel dank voor alles wat je me geeft: liefde, wijsheid, vertrouwen, kennis, rust en een goed glas wijn. We zijn complementair aan elkaar, maar delen ook dezelfde waarden, normen en interesses, waardoor we zo'n fijn team zijn. Als geen ander weet jij wat echt belangrijk is in het leven en weten wij samen dat we altijd het geluk zullen blijven ervaren. Ik hou van jou, onbeschrijfelijk veel.

CV

Amerins Weijenberg werd geboren op 1 maart 1982 in Drachten; haar naam verwijst naar de Friese wortels van haar familie. Ze groeide op met haar ouders en twee zusjes in het Brabantse Uden.

In 2000 behaalde zij haar diploma aan Gymnasium Bernrode te Heeswijk-Dinther. Aansluitend startte zij met haar studie Geneeskunde aan de Rijksuniversiteit Groningen. Tijdens de co-schappen in het Universitair Medisch Centrum Groningen en affiliaties werd haar interesse gewekt door de neurologie, en in het bijzonder de kinderneurologie.

Nadat zij in 2006 was afgestudeerd als arts, werkte ze als ANIOS neurologie in Isala Zwolle en het Elisabeth-TweeSteden Ziekenhuis te Tilburg.

In 2008 begon ze met haar opleiding tot neuroloog in het Universitair Medisch Centrum Groningen (opleider prof. dr. H.P.H. Kremer). Haar verdiepingsstage deed zij bij de kinderneurologie (opleider prof. dr. O.F. Brouwer). In de eindfase van de opleiding tot neuroloog startte zij met promotieonderzoek.

Na afronding van haar opleiding tot neuroloog in 2015 continueerde zij haar promotieonderzoek. Aansluitend werkte zij bij de algemene kindergeneeskunde in Isala Zwolle en rondde daarmee haar opleiding tot kinderneuroloog af in 2018.

Sinds 2019 werkt zij als kinderneuroloog bij SEIN (Stichting Epilepsie Instellingen Nederland) in Zwolle.

Amerins is heel gelukkig getrouwd met Hans de Graaf en zeer trotse moeder van Stije (2012), Lidewij (2014) en Deirdre (2016).